PAT T COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 08 March 2001 (08.03.01)	
International application No. PCT/US00/19524	**Applicant's or agent's file reference** 10365/07402
International filing date (day/month/year) 17 July 2000 (17.07.00)	**Priority date** (day/month/year) 15 July 1999 (15.07.99)
Applicant ARAD, Dorit et al	

1. The designated Office is hereby notified of its election made:

   [X] in the demand filed with the International Preliminary Examining Authority on:

   24 January 2001 (24.01.01)

   [ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

   [ ] was not

   made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer C. Cupello
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

COOPER, Rod, C.
Sidley Austin Brown & Wood
717 North Harwood, Suite 3400
Dallas, TX 75201-6507
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year) 29 octobre 2001 (29.10.01)	
Applicant's or agent's file reference 10365/07402	**IMPORTANT NOTIFICATION**
International application No. PCT/US00/19524	**International filing date** (day/month/year) 17 juillet 2000 (17.07.00)

1. The following indications appeared on record concerning:

[ ] the applicant [ ] the inventor [X] the agent [ ] the common representative

Name and Address

COOPER, Rod, C.
Sidley & Austin
717 North Harwood
Dallas, TX 75201
United States of America

State of Nationality:

State of Residence:

Telephone No.: 214-981-3300

Facsimile No.: 214-981-3400

Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] *the person* [ ] *the name* [X] *the address* [ ] *the nationality* [ ] *the residence*

Name and Address

COOPER, Rod, C.
Sidley Austin Brown & Wood
717 North Harwood, Suite 3400
Dallas, TX 75201-6507
United States of America

State of Nationality:

State of Residence:

Telephone No.: 214-981-3300

Facsimile No.: 214-981-3400

Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 *Geneva 20, Switzerland*** Facsimile No.: (41-22) 740.14.35	Authorized officer Beate GIFFO-SCHMITT Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994) 004408756

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70) 14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
10365/07402		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/19524	17/07/2000	15/07/1999
International Patent Classification (IPC) or national classification and IPC C07D305/00		
Applicant CYTOCLONAL PHARMACEUTICS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 42 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24/01/2001	05.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Helps, I Telephone No. +49 89 2399 8209

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/19524

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-3,5-50	as originally filed	
4,4a	with telefax of	09/05/2001

Claims, No.:

1-9	as originally filed	
10-23	with telefax of	09/05/2001

Drawings, sheets:

1/19-19/19	as originally filed	

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-6 (part).

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-6 (part).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;

citations and explanations supp rting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-23
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-23
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-23
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

V. CITATIONS AND EXPLANATIONS

The following documents are mentioned in this report.

US-A-5,674,905 (A)
US-A-5,658,940 (B)
US-A-4,349,552 (C)
US-A-5,302,589 (D)
Journal of the National Cancer Institute, vol.86, p.1517-24 (1994) (E)
Organic Letters, vol.1, p.43-6 (1999) (F)

The novel feature of claim 1 is the use of software to identify binding sites on a known anti-tumour composition and using the software to design a new anti-tumour composition with binding sites similar to the known composition. The dependent claims 2-6 are novel by consequence. The novel feature of claim 7 is the use of software to design an alternative composition having a central skeleton with three side chains having the parameters given in the claim. The dependent claims 8-11 are novel by consequence.

The novel feature of the norbornene compounds of claims 12, 14 and 15, and of the bicyclooctane compounds of claims 13 and 16, is the combination of R3 to R5 side chains which are represented by the listed structures. The dependent claims 17 to 23 are novel by consequence.

Claims 1 to 23 therefore meet the Novelty requirements of Article 33(2) PCT.

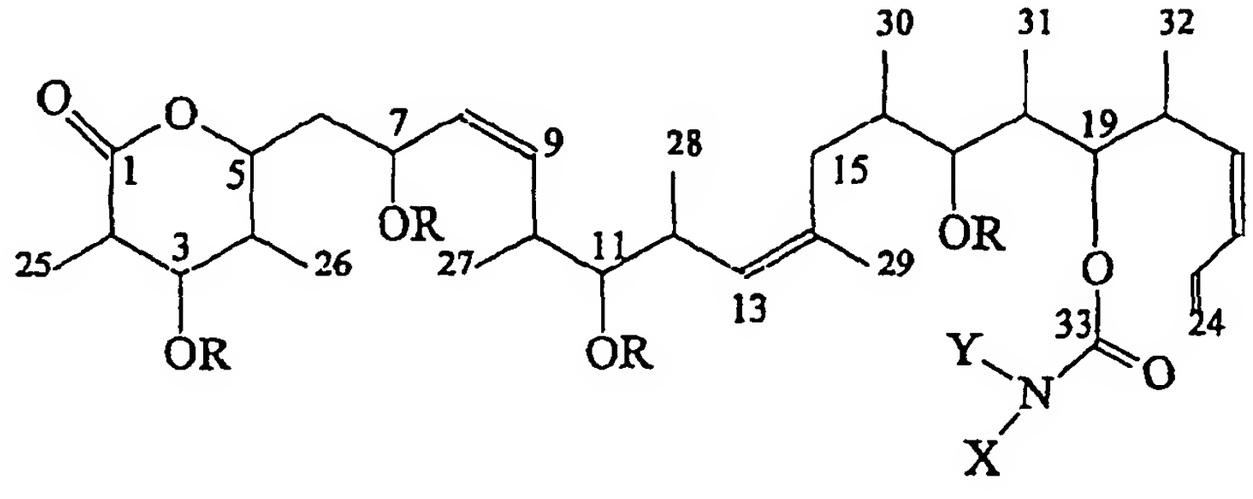
Document (E) describes the use of computer modelling to predict synergism or antagonism between various anti-cancer drugs, including paclitaxel. Document (F) describes the use of molecular modelling for predicting the binding of paclitaxel to microtubule receptors. Neither of these documents gives any information on the use of software to design alternative paclitaxel compositions by using three dimensional modelling. Document (A) discloses bicyclooctane and bicycloheptane derivatives and their use as CCK receptor ligands and the treatment of cancer. Documents (B) to (D)

describe maleimides, uracils and aza-androstenones for the treatment of cancer. Some of these moieties are included in the list of side chain groups in claims 12-23. Since the compounds of documents (A) to (D) are not structurally close to the compounds of claims 12-23, it would not have been obvious for the skilled man to prepare the presently claimed bicycloheptane and bicyclooctane derivatives in order to make available paclitaxel alternative compositions. Inventive step (Article 33(3) PCT) is recognised because the problem of preparing paclitaxel alternative compositions has been solved in a non obvious manner.

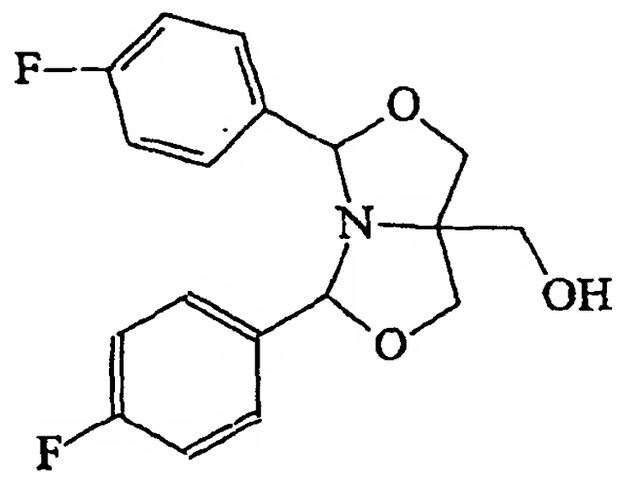
VIII CERTAIN OBSERVATIONS ON THE INTERNATIONAL APPLICATION

Claims 12 and 13 do not meet the clarity and conciseness requirements of Article 6 PCT due to the very long lists of substituents contained therein.

results in mitotic arrest," *Chem Biol* 3:287-293). The basic structure of discodermolide is as follows:



A synthetic anticancer agent known as GS-164 having the following chemical structure has been reported to stimulate microtubule polymerization.



Comparative conformational analysis reportedly indicated that the structure of GS-164 mimics the minimum essential sites of TAXOL® required to exhibit TAXOL®-like properties. (Shintani, et al. 1997. "GS-164, a small synthetic compound, stimulates tubulin polymerization by a similar mechanism to that of Taxol," *Cancer Chemother Pharmacol* 40:513-520.)

Disadvantages have also been associated with some paclitaxel derivatives. For example, many paclitaxel derivatives reported to date have not had the steric conformational properties of natural paclitaxel, nor has there been the ability to change the right side of the molecule by combinatorial chemistry with carbohydrates, calcium chelators, or oxygenated small molecules.

Other compounds with similar structures to taxane are disclosed as possessing numerous activities. In U.S. 4,349,552 5-fluorouracil derivatives useful for treating cancer are disclosed. In U.S. 5,302,589 heterocyclic inhibitors of 5-alpha-testosterone

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
10365/07402		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/19524	17/07/2000	15/07/1999
Applicant		
CYTOCLONAL PHARMACEUTICS, INC.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/US 00/19524

Box I Observati ns where certain claims were found unsearchabl (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-6(part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-6(part)

Due to the large scope of these claims a complete search is not possible within a reasonable time limit. The search was limited to the scope covered by the description, which covers the design and synthesis of paclitaxel alternative compositions (see Guidelines, B-III, 3.7).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/19524

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C271/22 C07D493/04 C07C69/78 C07C235/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 674 905 A (KALINDJIAN ET. AL.) 7 October 1997 (1997-10-07) claims; examples ---	12,13
A	US 5 658 940 A (MULLER ET. AL.) 19 August 1997 (1997-08-19) claims; examples ---	12,13
A	US 4 349 552 A (TAKAYA ET. AL.) 14 September 1982 (1982-09-14) column 1, line 10 - line 18; claims; examples ---	12,13
A	US 5 302 589 A (FRYE ET. AL.) 12 April 1994 (1994-04-12) claim 1 --- -/--	12,13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 February 2001	26.03.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Helps, I

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	TING-CHAO CHOU ET. AL.: "Computerised Quantitation of Synergism and Antagonism of Taxol, Topotecan and Cisplatin Against Human Teratocarcinoma Cell Growth. " JOURNAL OF THE NATIONAL CANCER INSTITUTE , vol. 86, no. 20, 19 October 1994 (1994-10-19), pages 1517-24, XP000983664 whole article ---	1-11
A	M. WANG ET. AL.: "A Unified and Quantitative Receptor Model for the Microtubule Binding of Paclitaxel and Epothilone." ORGANIC LETTERS, vol. 1, no. 1, January 1999 (1999-01), pages 43-6, XP000983329 whole article -----	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/19524

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5674905 A	07-10-1997	GB 2268739 A	19-01-1994
		AU 4348993 A	24-01-1994
		DE 69313649 D	09-10-1997
		EP 0655053 A	31-05-1995
		WO 9400421 A	06-01-1994
		MX 9303670 A	31-05-1994
US 5658940 A	19-08-1997	AU 723915 B	07-09-2000
		AU 7387396 A	28-04-1997
		CA 2233975 A	10-04-1997
		CZ 9801053 A	15-07-1998
		EP 0862552 A	09-09-1998
		FI 980776 A	05-06-1998
		HU 9902034 A	29-11-1999
		JP 11513387 T	16-11-1999
		PL 326063 A	17-08-1998
		SK 44698 A	09-09-1998
		WO 9712859 A	10-04-1997
US 4349552 A	14-09-1982	AT 1011 T	15-05-1982
		DE 2962834 D	01-07-1982
		EP 0010941 A	14-05-1980
		ES 8100275 A	16-01-1981
		JP 55081865 A	20-06-1980
US 5302589 A	12-04-1994	US 5457098 A	10-10-1995

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 January 2001 (25.01.2001)

PCT

(10) International Publication Number
WO 01/05779 A3

(51) International Patent Classification[7]: C07C 271/22, C07D 493/04, C07C 69/78, 235/14

(21) International Application Number: PCT/US00/19524

(22) International Filing Date: 17 July 2000 (17.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/143,973	15 July 1999 (15.07.1999)	US
60/171,892	23 December 1999 (23.12.1999)	US

(71) Applicant *(for all designated States except US)*: **CYTOCLONAL PHARMACEUTICS, INC.** [US/US]; 9000 Harry Hines Boulevard, Suite 621, Dallas, TX 75235 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ARAD, Dorit** [IL/US]; 16901 Park Hill Drive, Dallas, TX 75248 (US). **BOLLON, Arthur, P.** [US/US]; 13227 Cedar Lane, Dallas, TX 75234 (US). **POLAND, Bradley, W.** [US/US]; 2804 Daybreak Drive, Dallas, TX 75287 (US). **YOUNG, David, C.** [US/US]; 5401 Buckner Court, Flower Mound, TX 75028 (US).

(74) Agents: **COOPER, Rod, C.** et al.; Sidley & Austin, 717 North Harwood, Dallas, TX 75201 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
16 August 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/05779 A3

(54) Title: METHOD OF DESIGNING TUBULIN POLYMERIZATION STABILIZERS

(57) Abstract: A method for designing paclitaxel alternative compounds which stabilize the tubulin polymerization process has been found. These compounds in solution possess steric conformational properties of natural paclitaxel and are capable of binding to the tubulin protein at the same site where paclitaxel is known to bind. The compounds of the present invention stabilize tubulin polymerization in a way that is mechanistically equivalent to activity mechanism of paclitaxel. The compounds of the present invention have increased solubility, simpler synthesis, and the possibility for specificity and optimization due to the combinatorial reactions over natural paclitaxel.

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/US 00/19524

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C271/22 C07D493/04 C07C69/78 C07C235/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 674 905 A (KALINDJIAN ET. AL.) 7 October 1997 (1997-10-07) claims; examples ---	12,13
A	US 5 658 940 A (MULLER ET. AL.) 19 August 1997 (1997-08-19) claims; examples ---	12,13
A	US 4 349 552 A (TAKAYA ET. AL.) 14 September 1982 (1982-09-14) column 1, line 10 - line 18; claims; examples ---	12,13
A	US 5 302 589 A (FRYE ET. AL.) 12 April 1994 (1994-04-12) claim 1 --- -/--	12,13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 February 2001	26. 03. 01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Helps, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/US 00/19524

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	TING-CHAO CHOU ET. AL.: "Computerised Quantitation of Synergism and Antagonism of Taxol, Topotecan and Cisplatin Against Human Teratocarcinoma Cell Growth. " JOURNAL OF THE NATIONAL CANCER INSTITUTE , vol. 86, no. 20, 19 October 1994 (1994-10-19), pages 1517-24, XP000983664 whole article ---	1-11
A	M. WANG ET. AL.: "A Unified and Quantitative Receptor Model for the Microtubule Binding of Paclitaxel and Epothilone." ORGANIC LETTERS, vol. 1, no. 1, January 1999 (1999-01), pages 43-6, XP000983329 whole article -----	1-11

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/19524

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-6(part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-6(part)

Due to the large scope of these claims a complete search is not possible within a reasonable time limit. The search was limited to the scope covered by the description, which covers the design and synthesis of paclitaxel alternative compositions (see Guidelines, B-III, 3.7).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ional Application No
PCT/US 00/19524

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5674905 A	07-10-1997	GB 2268739 A	19-01-1994
		AU 4348993 A	24-01-1994
		DE 69313649 D	09-10-1997
		EP 0655053 A	31-05-1995
		WO 9400421 A	06-01-1994
		MX 9303670 A	31-05-1994
US 5658940 A	19-08-1997	AU 723915 B	07-09-2000
		AU 7387396 A	28-04-1997
		CA 2233975 A	10-04-1997
		CZ 9801053 A	15-07-1998
		EP 0862552 A	09-09-1998
		FI 980776 A	05-06-1998
		HU 9902034 A	29-11-1999
		JP 11513387 T	16-11-1999
		PL 326063 A	17-08-1998
		SK 44698 A	09-09-1998
		WO 9712859 A	10-04-1997
US 4349552 A	14-09-1982	AT 1011 T	15-05-1982
		DE 2962834 D	01-07-1982
		EP 0010941 A	14-05-1980
		ES 8100275 A	16-01-1981
		JP 55081865 A	20-06-1980
US 5302589 A	12-04-1994	US 5457098 A	10-10-1995

reductase are disclosed. Novel succinimides and maleimides that inhibit cytokines are described in U.S. 5,658,940. Lastly, bicyclooctane and bicycloheptane derivatives reportedly act as ligands to CCK and gastrin receptors in U.S. 5,674,905.

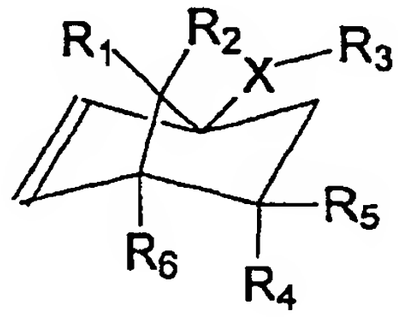
In addition to there being compounds with a similar structure to taxane, there are also existing computational methods to study paclitaxel's binding site with tubulin and its therapeutic effect. Because epothilones compete against paclitaxel for microtubule binding, the paclitaxel binding site of tubulin was modeled with suitable epothilone conformers to better understand how epothilone interacts with tubulin (Wang, M., et al. 1999. "A unified and quantitative receptor model for the microtubule binding of paclitaxel and eopthilone," *Organic Letters* 1:43-46). The in vitro synergistic effects on teratocarcinoma of paclitaxel with other drugs used to treat cancer were modeled computationally to propose new doseages when these drugs are co-administered (Chou, T-C., et al. 1994. "Computerized quantitation of synergism and antagonism of Taxol, Topotecan, and Cisplatin against human teratocarcinoma cell growth: a rational approach to clinical protocol design," *J Natl Can Inst* 86:1517-1524).

A method has been found by which compounds exhibiting paclitaxel-like activity and having distinct advantages over paclitaxel and known derivatives can be synthesized.

10. The method of Claim 7, wherein said sp^3 oxygen is positioned in space to simulate the position of the oxetane ring of paclitaxel.

11. The method of Claims 7-11 further comprising synthesizing said alternative composition.

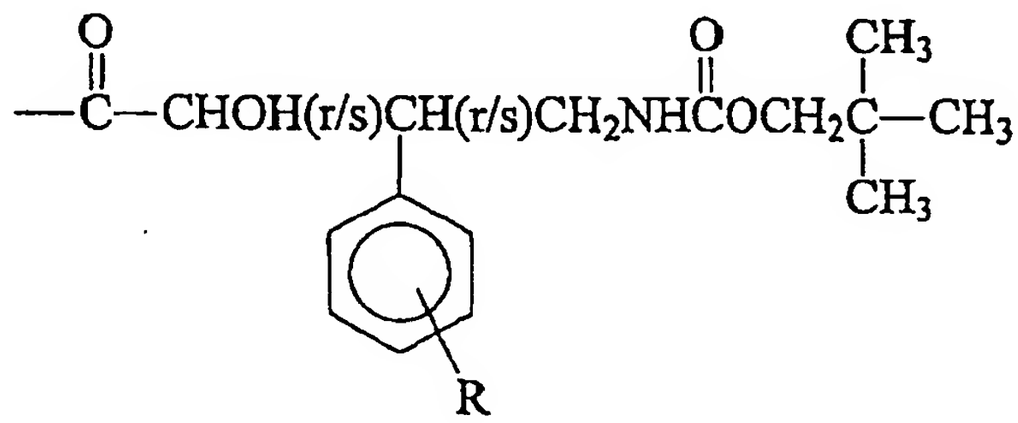
12. A paclitaxel compound having a chemical structure

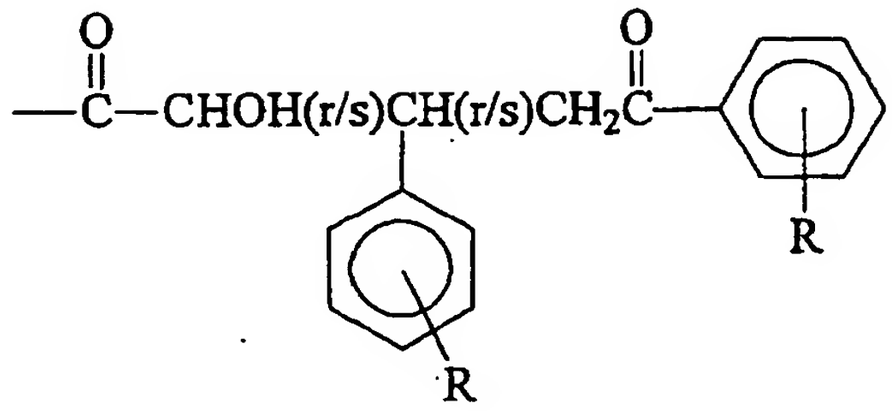


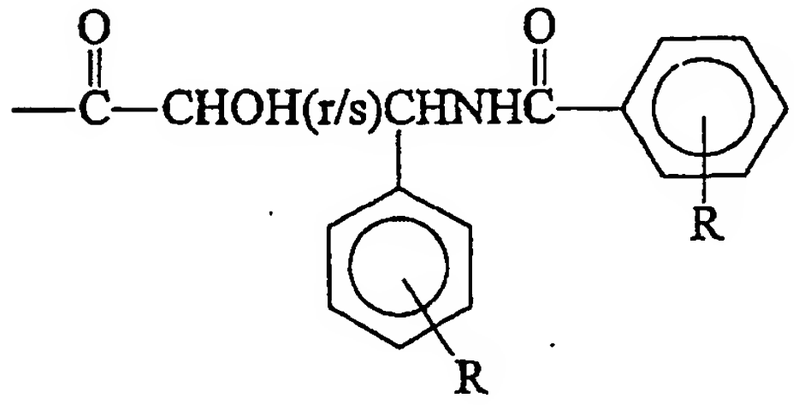
wherein R_1 and R_2 are selected from the group consisting of: hydrogen, methyl, acetyl, ethyl, C_1 - C_4 aliphatic chain and substituted C_1 - C_6 aliphatic chain, wherein said substituted aliphatic chain is substituted once or twice with functional groups selected from the group consisting of: amide, ketone, hydroxy, phenyl, carboxylic acid, and an amino acid;

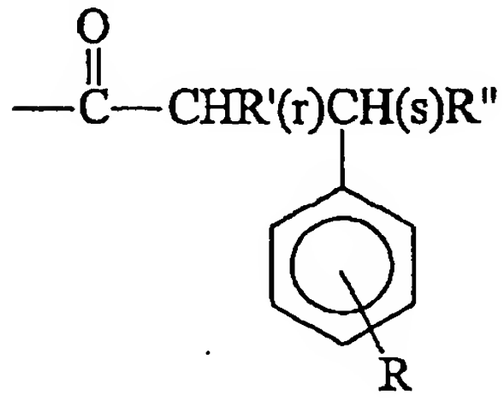
wherein X is selected from the group consisting of: O; CH_2; NH; S; S-CH_2; O-CH_2; or none;

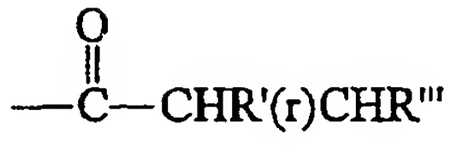
wherein R_3 is selected from the group consisting of:

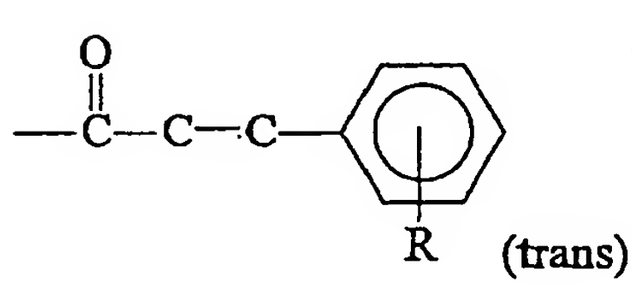




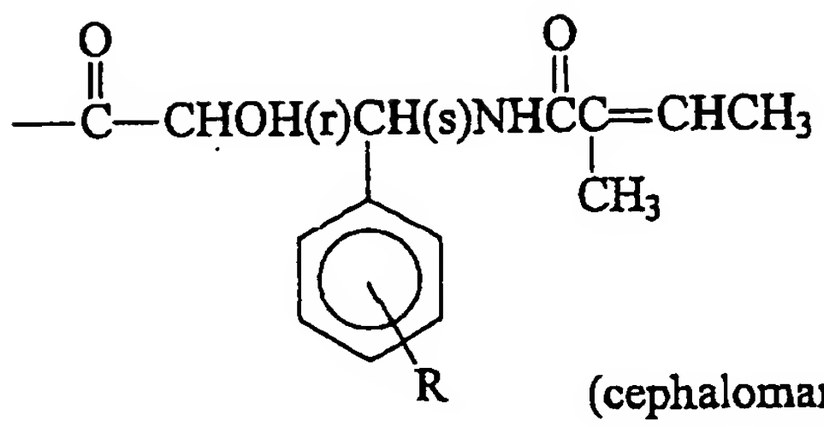




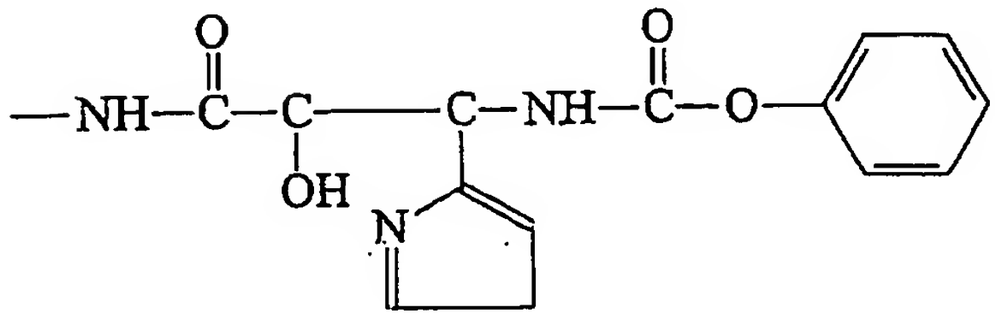


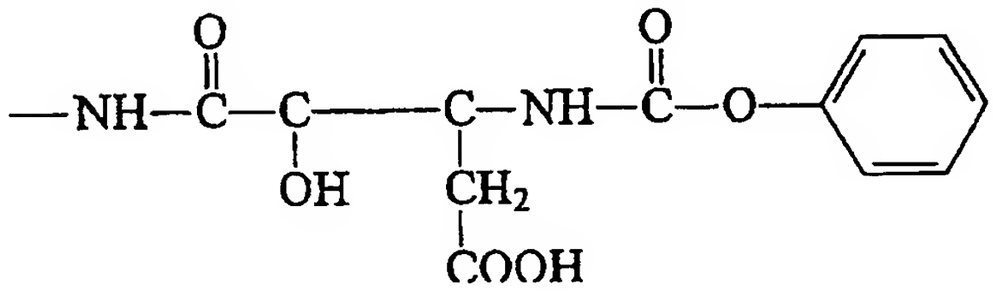


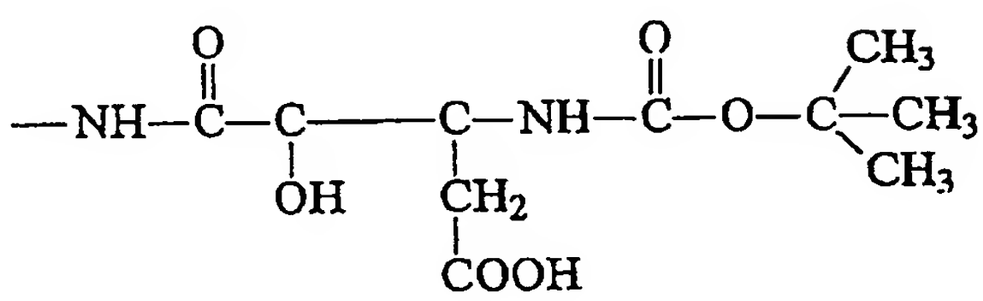
(trans)

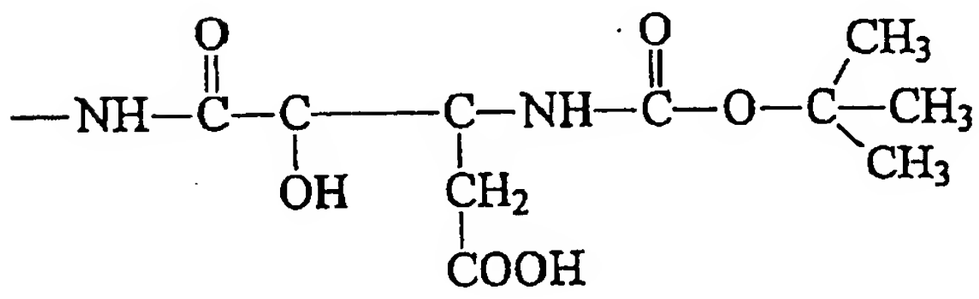


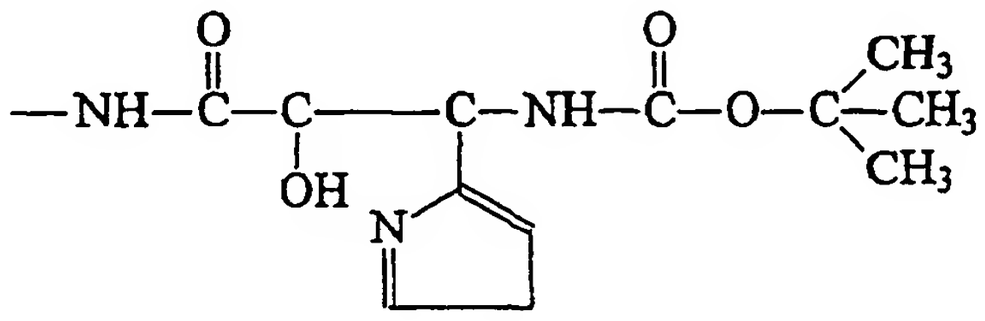
(cephalomannine)





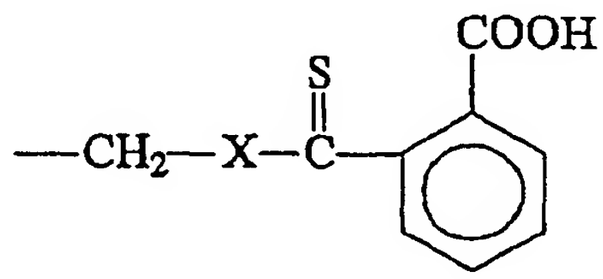


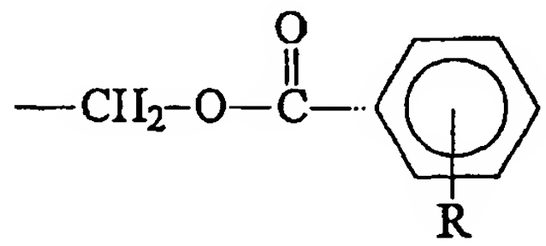


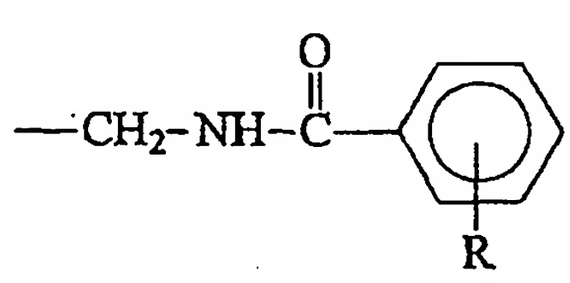


wherein the aryl rings are unsubstituted or singly, doubly, or triply substituted with R selected from the group consisting of: H, OH, and an electron withdrawing substituent;wherein R' is sclcctcd from the group consisting of: OH and H; wherein R" is selected from the group consisting of: NHBOC and H; wherein R"' is selected from the group consisting of: singly or doubly substituted aryl and fused aromatic ring;

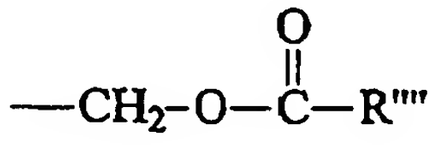
wherein R_4 is selected from thc group consisting of:



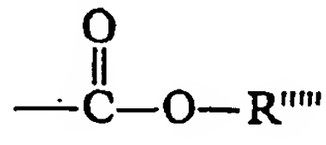




wherein the aromatic ring is singly, doubly, or triply substituted with any electron-withdrawing substituent compatible with the system which provides a lower energy gap in a π - π interaction;

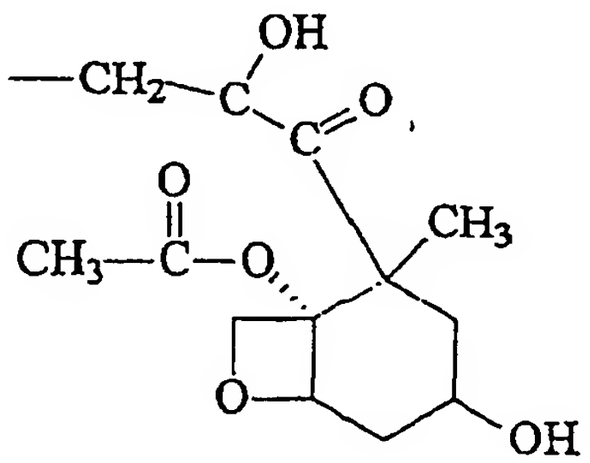


wherein R"" is a fixed aromatic ring or a fused aromatic ring substituted any electron-withdrawing substituent compatible with the system which provides a lower energy gap in a π - π interaction;



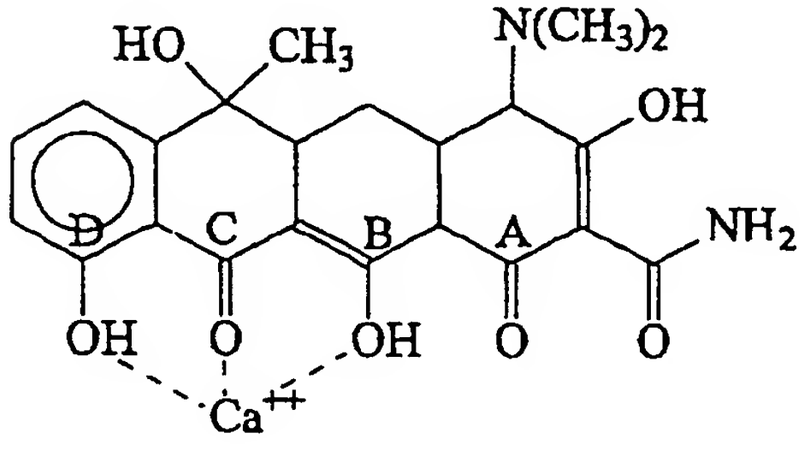
wherein R""" is selected from the group consisting of: H, cyclopropane, C_1-C_3 hydrocarbon chain, and C_1-C_3 substituted hydrocarbon chain wherein said substituted hydrocarbon chain is substituted with any electron-withdrawing substituent compatible with the system which provides a lower energy gap in a π - π interaction;

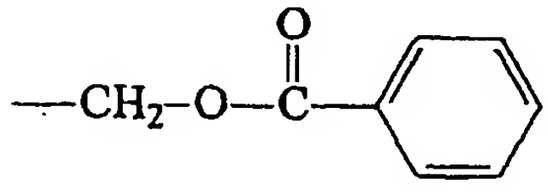
wherein R_5 is selected from the group consisting of:

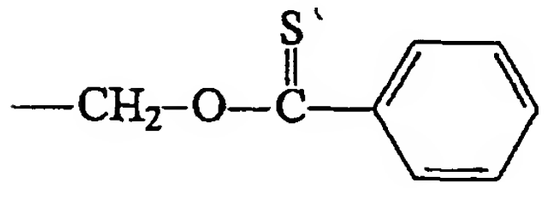


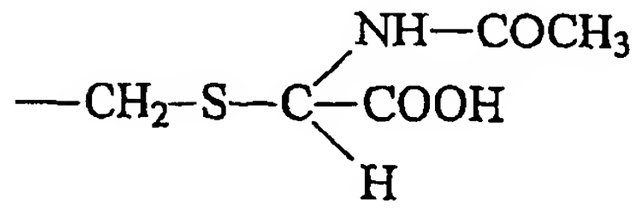
H, CH_3, C_1-C_5 hydrocarbon chain, C_1-C_5 substituted hydrocarbon chain, small hydrocarbon ring or heterocyclic ring, small substituted hydrocarbon ring or heterocyclic ring, citric acid and derivatives thereof, acetic acid and derivatives thereof, ascorbic acid and derivatives thereof, glucouroic acid or derivatives thereof, lactose, sialic acid, monosaccharides or

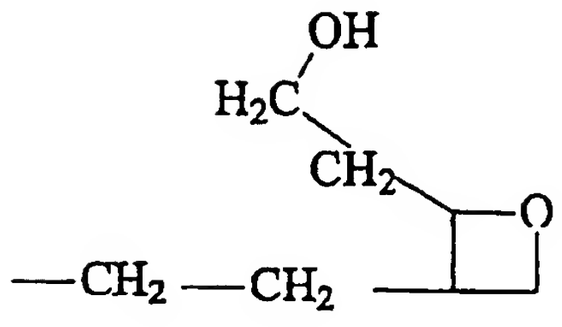
disaccharides of glyceraldehyde, erythrose, threose, ribose, arabinose xylose lyxose, allose, altrose, glucose, mannose, gulose, idose, galactose, talose, or their acidic ketose, alditol or inositol forms, calcium chelating molecule, oxygenated small molecule, any organic molecule that exhibits calcium-binding properties similar to tetracyclin



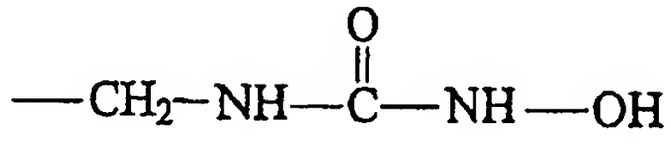


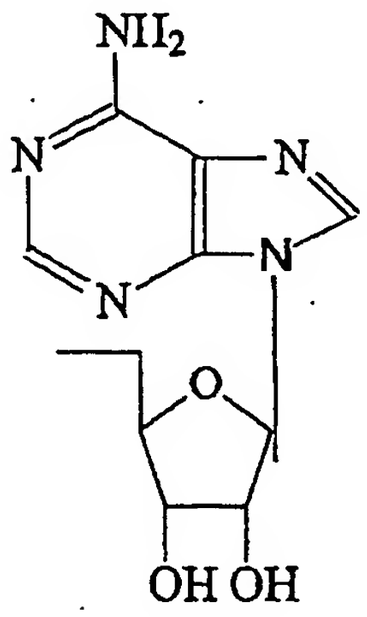


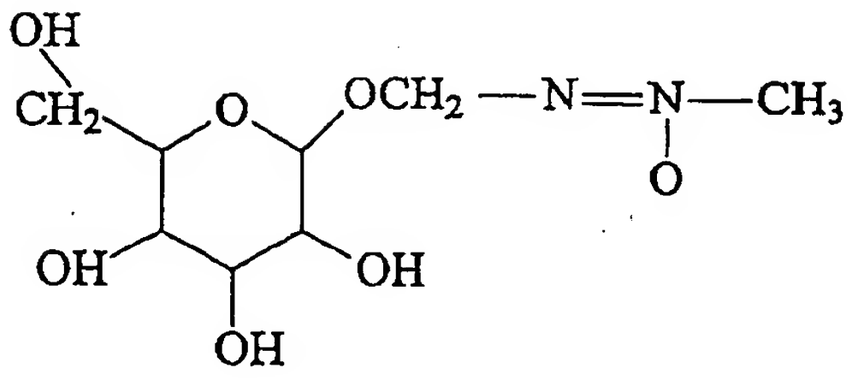




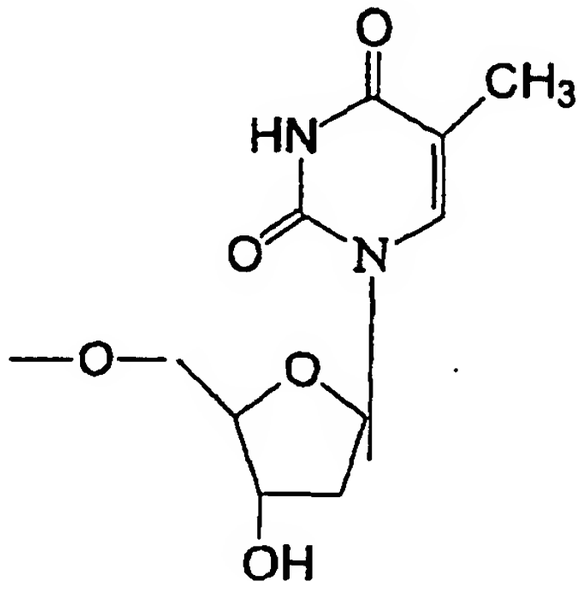
80



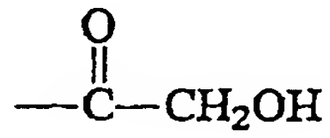


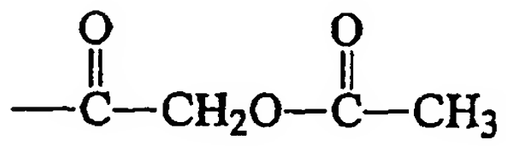


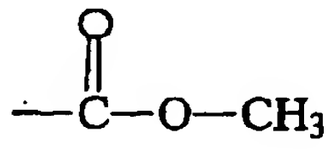
85



wherein R_6 is selected from the group consisting of:

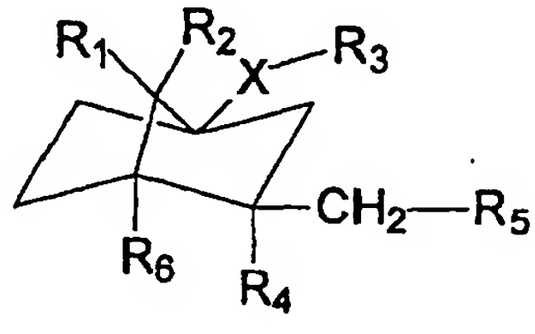






H, CH_3, OH, amine, C_1-C_5 carbo-aliphatic chain substituted with two or three of the following groups selected from the group consisting of: keto, hydroxy, sulfoxy, amide, an amino acid, and ethers of the form -CH_2-O-$(CH_2)_n$-CH_3 where n=1-5, wherein the right hand hydrocarbon chain is unsubstituted or substituted with 1 to 5 -OH or carbonyl groups.

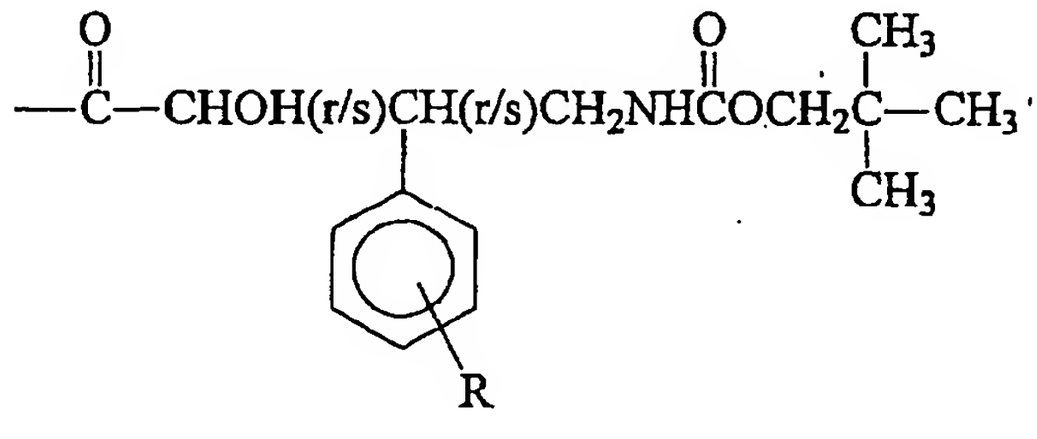
13. A paclitaxel compound having a chemical structure

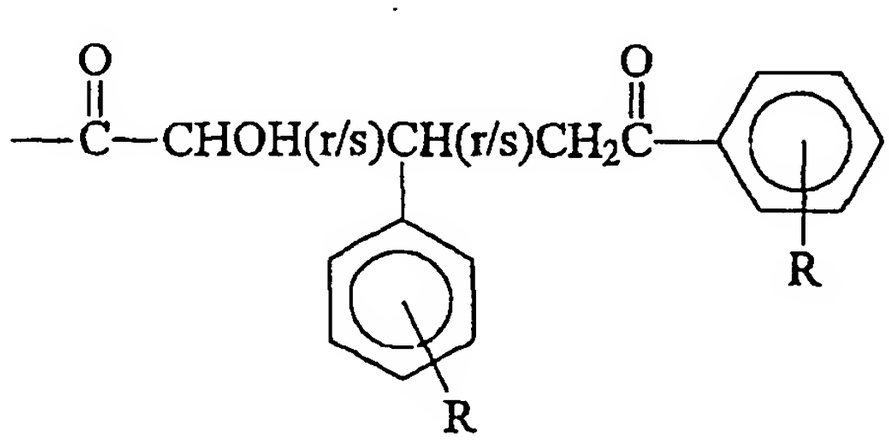


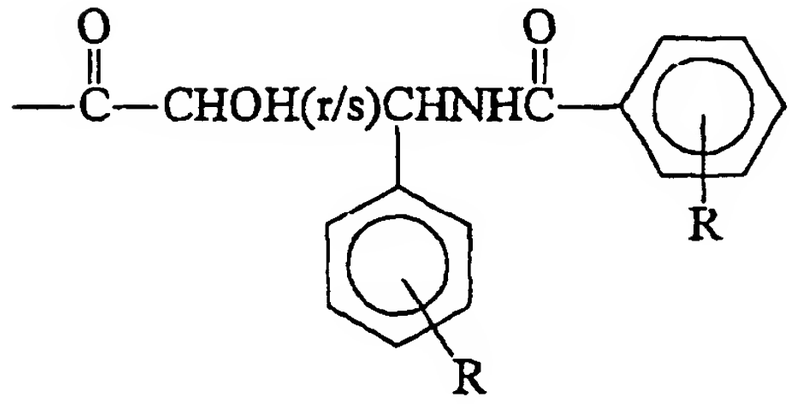
wherein R_1 and R_2 are selected from the group consisting of: hydrogen, methyl, acetyl, ethyl, C_1 - C_4 aliphatic chain and substituted C_1 - C_6 aliphatic chain, wherein said substituted aliphatic chain is substituted once or twice with functional groups selected from the group consisting of: amide, ketone, hydroxy, phenyl, carboxylic acid, and an amino acid;

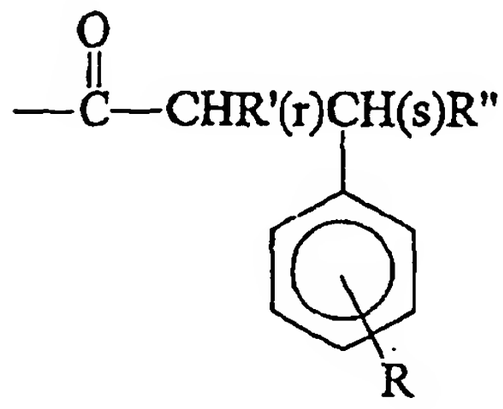
wherein X is selected from the group consisting of: O; CH_2; NH; S; S-CH_2; O-CH_2; or none;

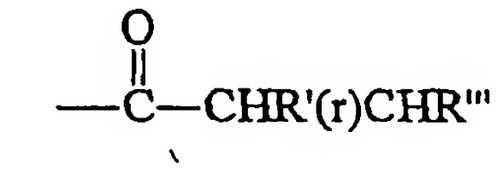
wherein R_3 is selected from the group consisting of:

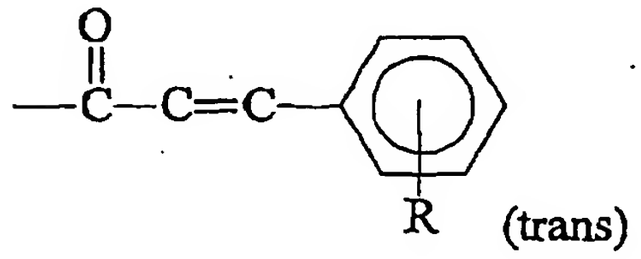


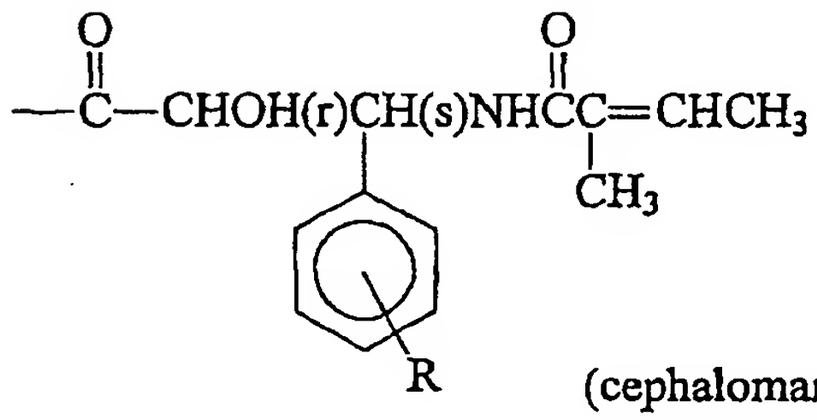




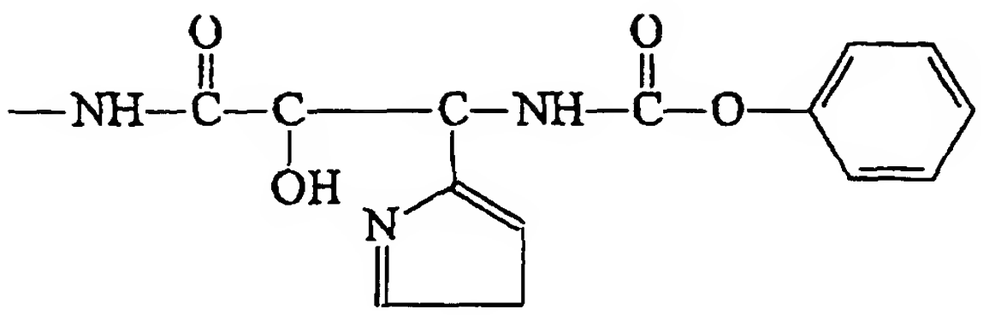


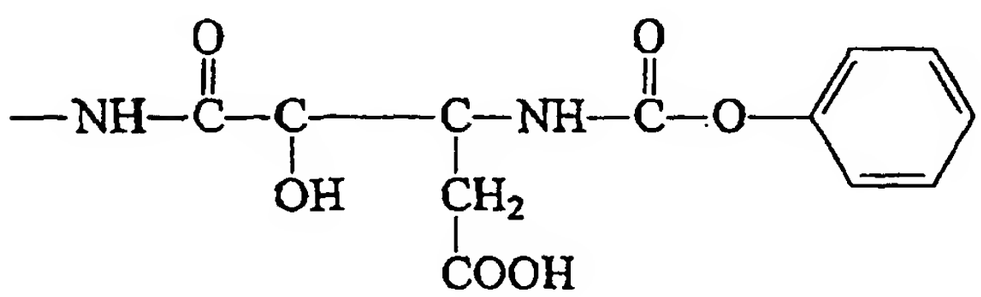


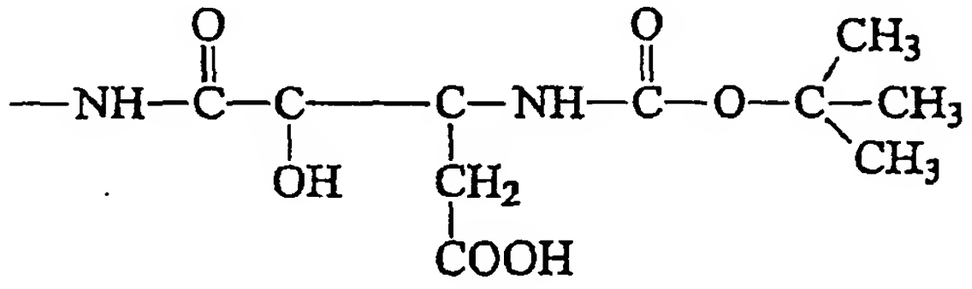


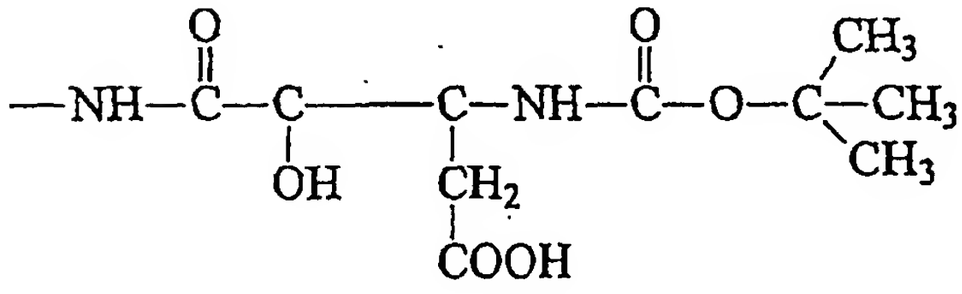


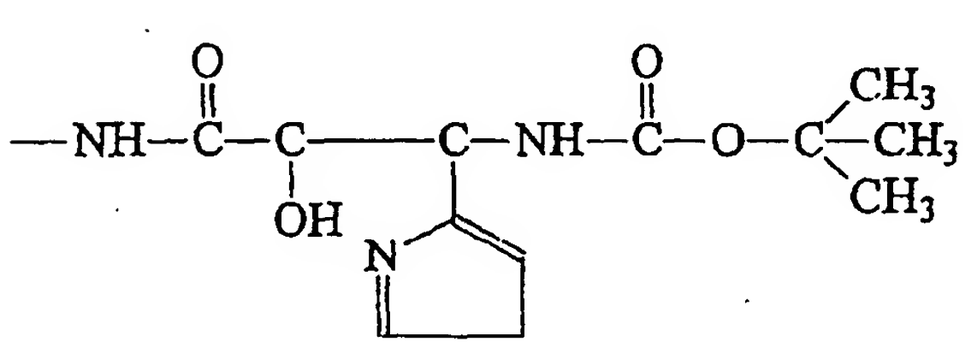
(cephalomannine)







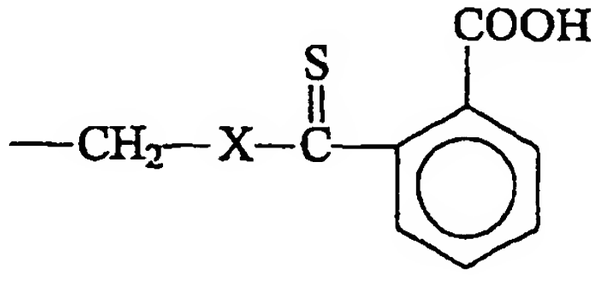


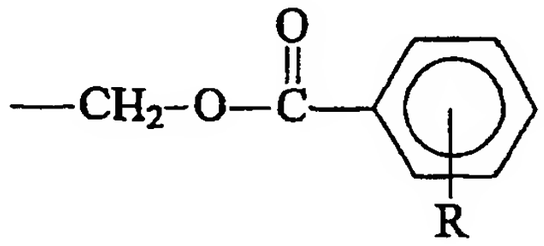


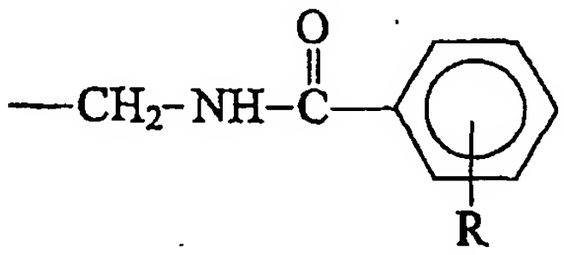
wherein the aryl rings are unsubstituted or singly, doubly, or triply substituted with R selected from the group consisting of: H, OH, and an electron withdrawing substituent; wherein R' is selected from the group consisting of: OH and H; wherein R" is selected from the group

consisting of: NHBOC and H; wherein R''' is selected from the group consisting of: singly or doubly substituted aryl and fused aromatic ring;

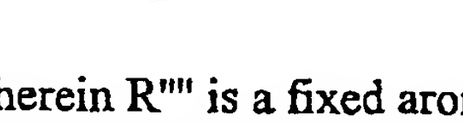
wherein R_4 is selected from the group consisting of:



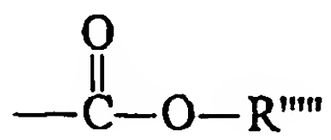


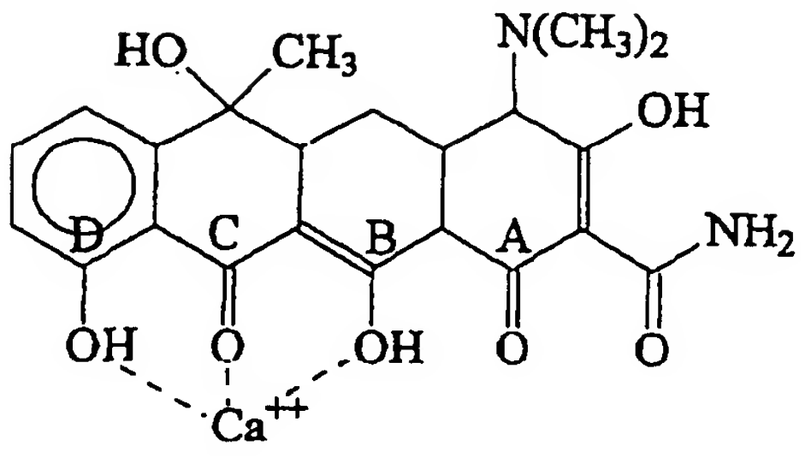


wherein the aromatic ring is singly, doubly, or triply substituted with any electron-withdrawing substituent compatible with the system which provides a lower energy gap in a π - π interaction;

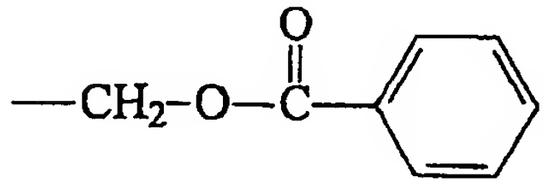


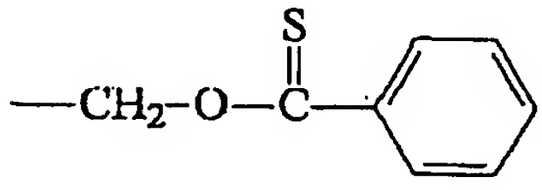
wherein R'''' is a fixed aromatic ring or a fused aromatic ring substituted with any electron-withdrawing substituent compatible with the system which provides a lower energy gap in a π - π interaction;



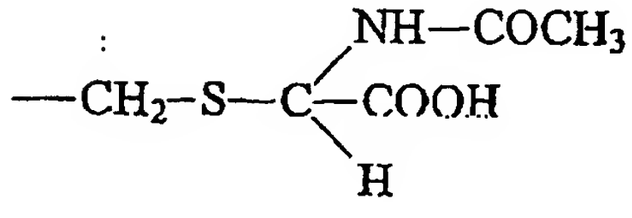


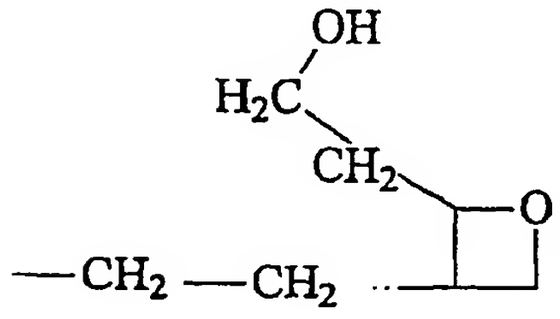
70



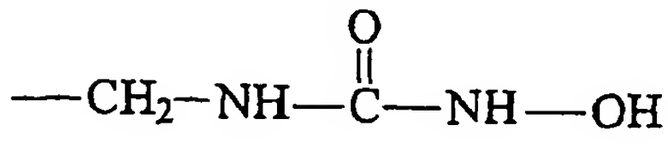


75



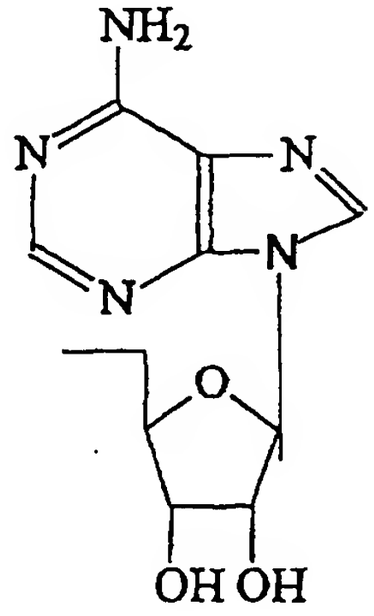


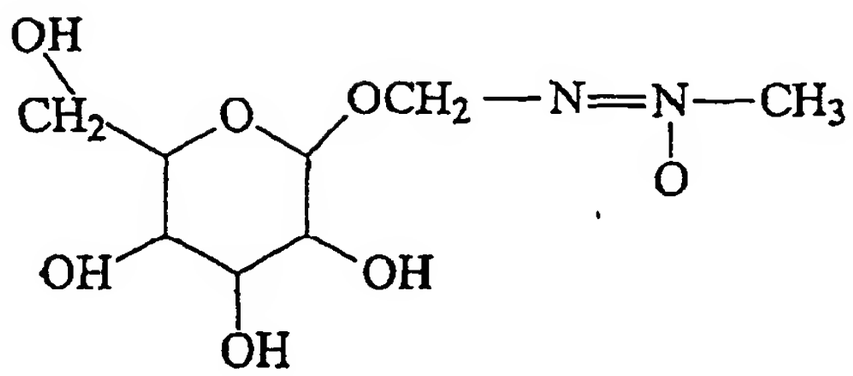
80



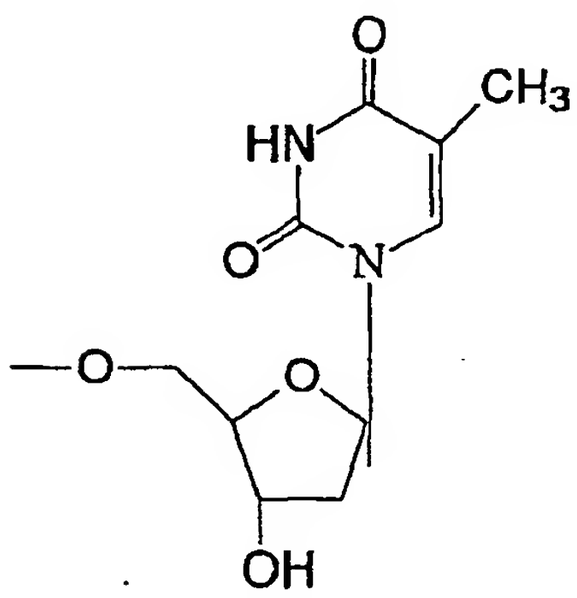
Empfangszeit 5.Sep. 22:17

AMENDED SHEET

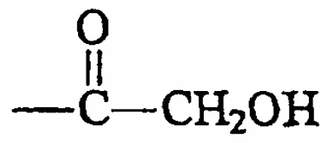


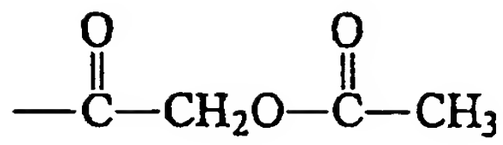


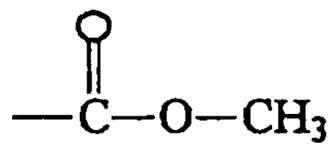
85



wherein R_6 is selected from the group consisting of:





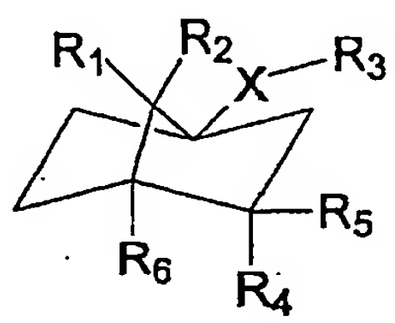


90

H, CH_3, OH, amine, C_1-C_5 carbo-aliphatic chain substituted with two or three of the following groups selected from the group consisting of: keto, hydroxy, sulfoxy, amide, an amino acid, ethers of the form -CH_2-O-$(CH_2)_n$-CH_3 where n=1-5, wherein the right hand hydrocarbon chain is unsubstituted or substituted with 1 to 5 -OH or carbonyl groups.

95

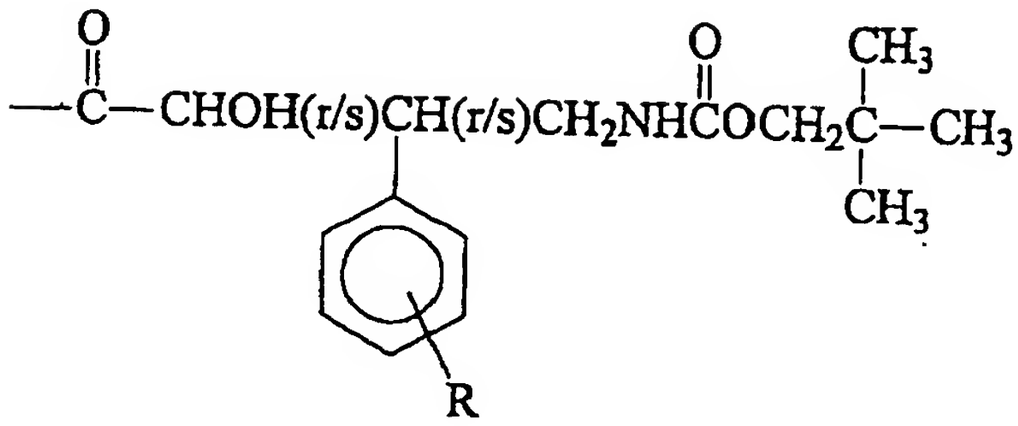
14. A paclitaxel compound having a chemical structure

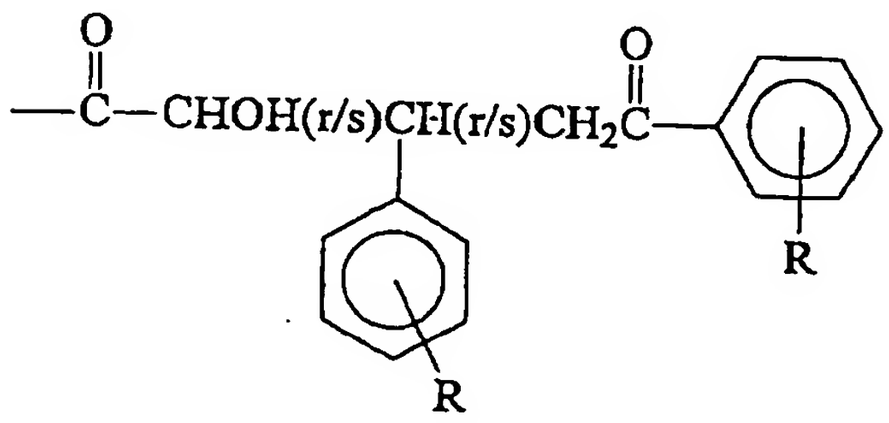


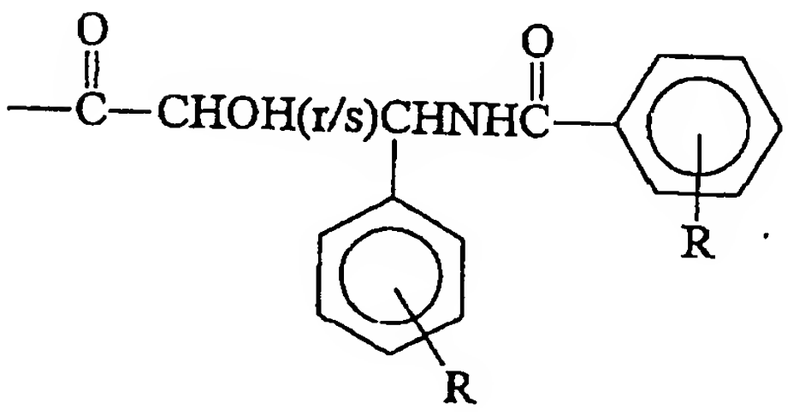
wherein R_1 and R_2 are selected from the group consisting of: hydrogen, methyl, acetyl, ethyl, C_1 - C_4 aliphatic chain and substituted C_1 - C_6 aliphatic chain, wherein said substituted aliphatic chain is substituted once or twice with functional groups selected from the group consisting of: amide, ketone, hydroxy, phenyl, carboxylic acid, and an amino acid;

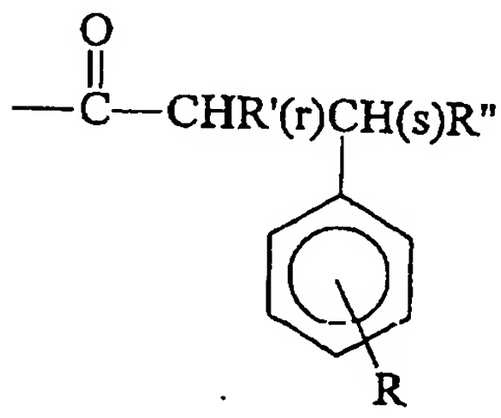
wherein X is selected from the group consisting of: O; CH_2; NH; S; S-CH_2; O-CH_2; or none;

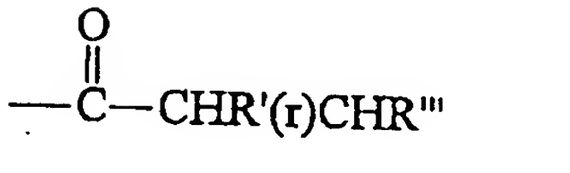
wherein R_3 is selected from the group consisting of:

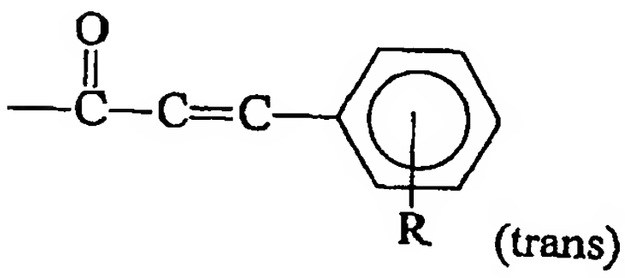


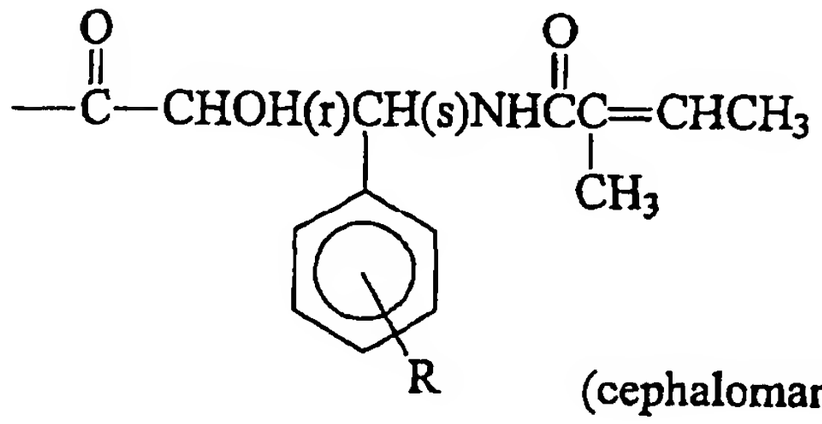




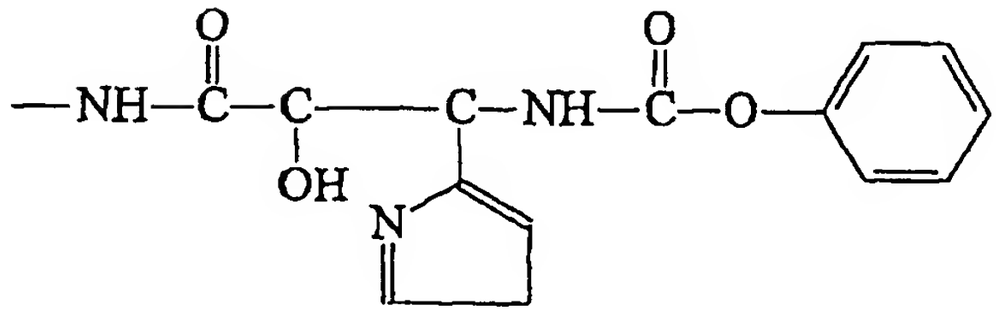


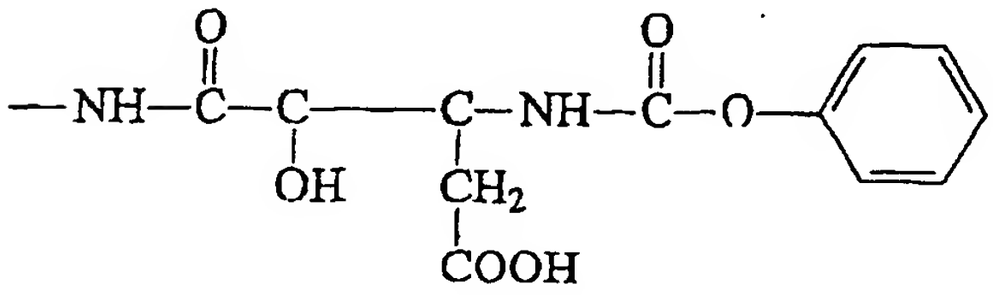


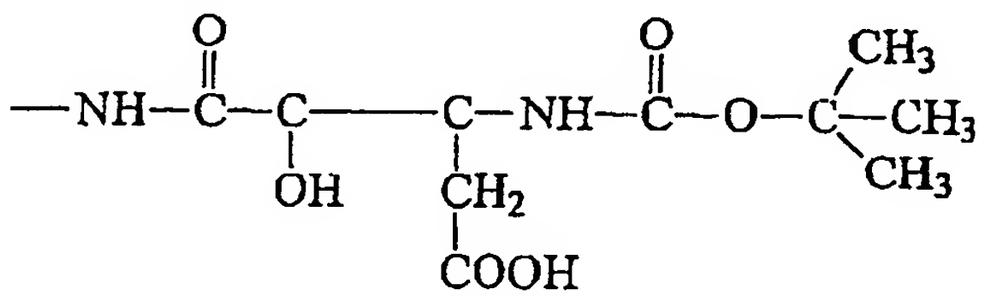

(trans)

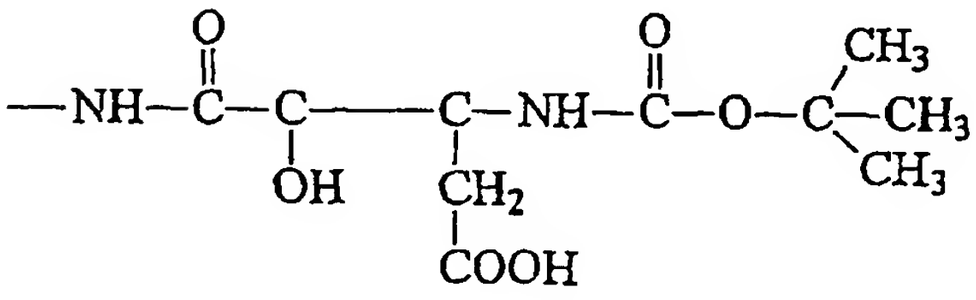


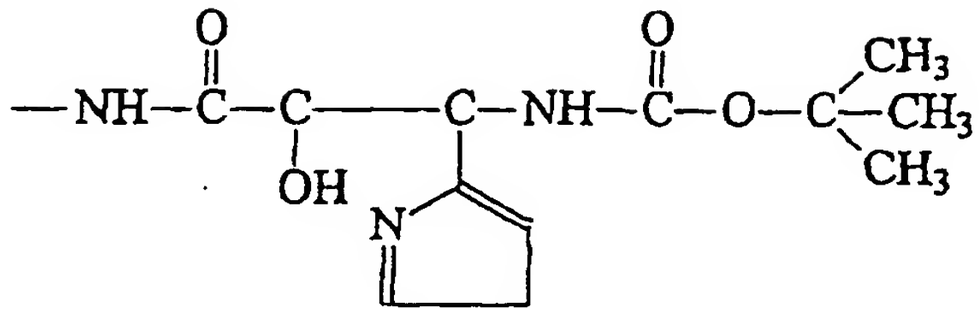
(cephalomannine)





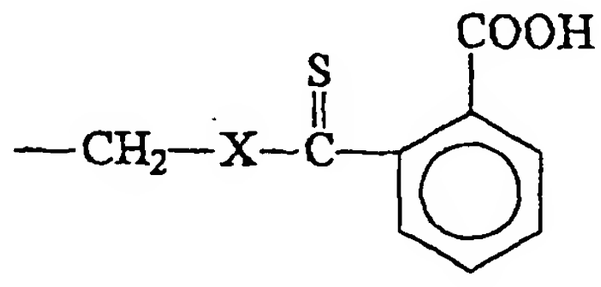


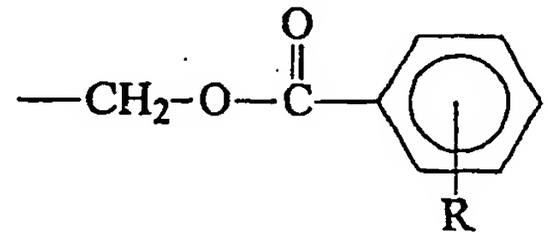


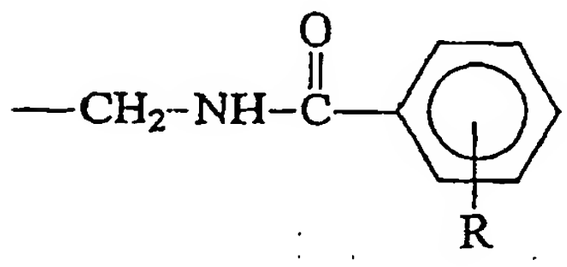


wherein the aryl rings are unsubstituted or singly, doubly, or triply substituted with R selected from the group consisting of: H, OH, and an electron withdrawing substituent;wherein R' is selected from the group consisting of: OH and H; wherein R" is selected from the group consisting of: NHBOC and H; wherein R"' is selected from the group consisting of: singly or doubly substituted aryl and fused aromatic ring;

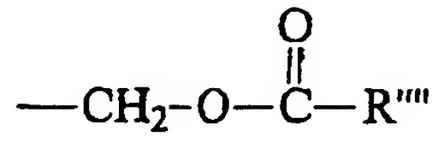
wherein R_4 is selected from the group consisting of:



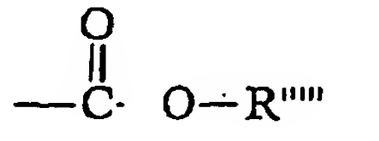




wherein the aromatic ring is singly, doubly, or triply substituted with any electron-withdrawing substituent compatible with the system which provides a lower energy gap in a π - π interaction;

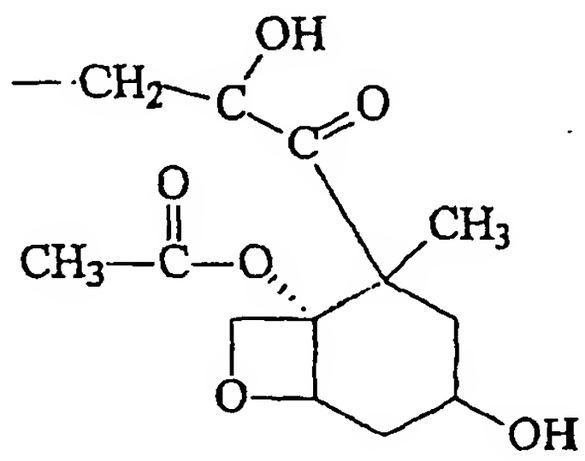


wherein R"" is a fixed aromatic ring or a fused aromatic ring substituted with R any electron-withdrawing substituent compatible with the system which provides a lower energy gap in a π - π interaction;



wherein R"" is selected from the group consisting of: H, cyclopropane, C_1-C_3 hydrocarbon chain, and C_1-C_3 substituted hydrocarbon chain wherein said substituted hydrocarbon chain is substituted with any electron-withdrawing substituent compatible with the system which provides a lower energy gap in a π - π interaction;

wherein R_5 is selected from the group consisting of:

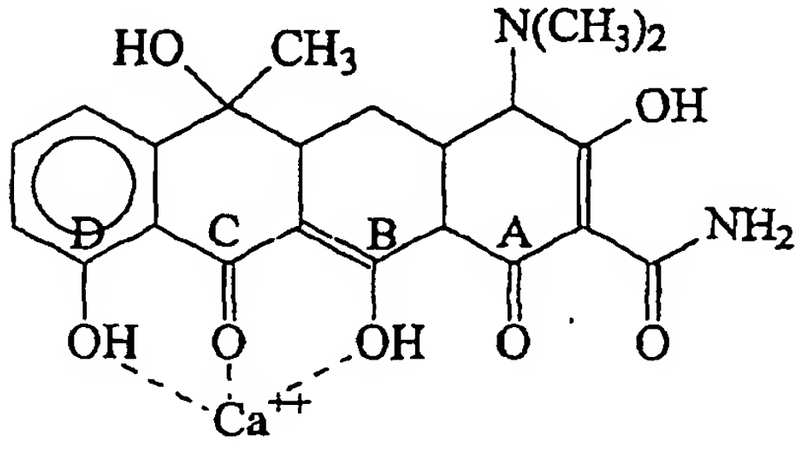


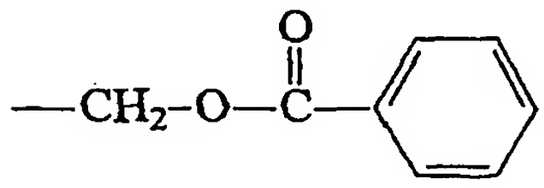
H, CH_3, C_1-C_5 hydrocarbon chain, C_1-C_5 substituted hydrocarbon chain, small hydrocarbon ring or heterocyclic ring, small substituted hydrocarbon ring or heterocyclic ring, citric acid and derivatives thereof, acetic acid and derivatives thereof, ascorbic acid and derivatives thereof, glucouroic acid or derivatives thereof, lactose, sialic acid, monosaccharides or

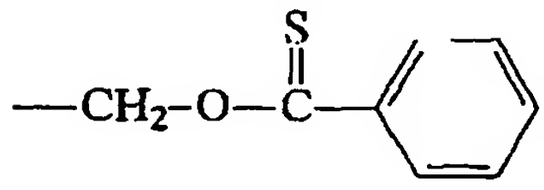
Empfangszeit 5.Sep. 22:17

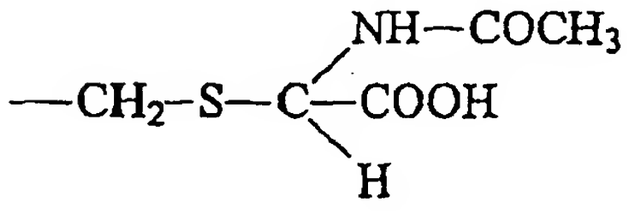
AMENDED SHEET

disaccharides of glyceraldehyde, erythrose, threose, ribose, arabinose xylose lyxose, allose, altrose, glucose, mannose, gulose, idose, galactose, talose, or their acidic ketose, alditol or inositol forms, calcium chelating molecule, oxygenated small molecule, any organic molecule that exhibits calcium-binding properties similar to tetracyclin



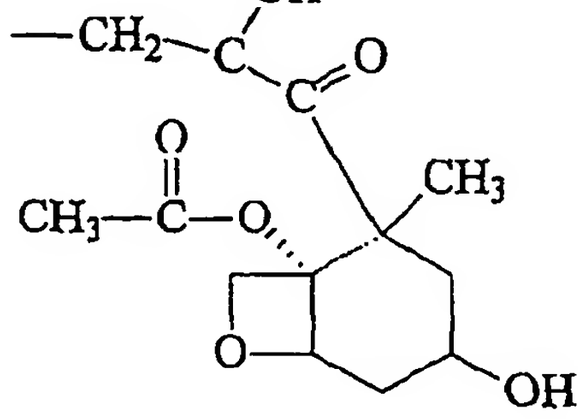




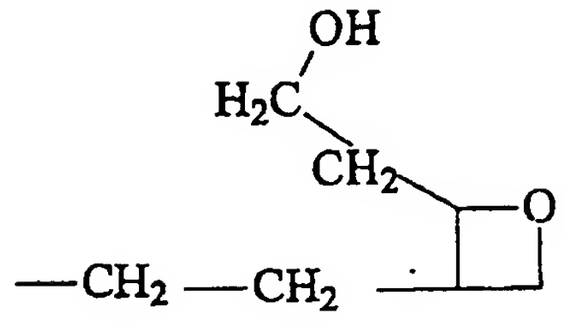


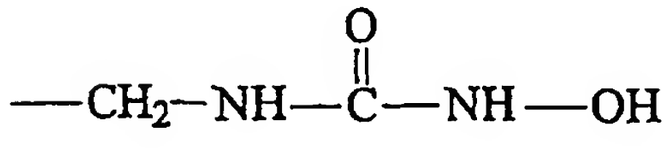
wherein R'''' is selected from the group consisting of: H, cyclopropane, C_1-C_3 hydrocarbon chain, and C_1-C_3 substituted hydrocarbon chain wherein said substituted hydrocarbon chain is substituted with any electron-withdrawing substituent compatible with the system which provides a lower energy gap in a π - π interaction;

wherein R_5 is selected from the group consisting of:

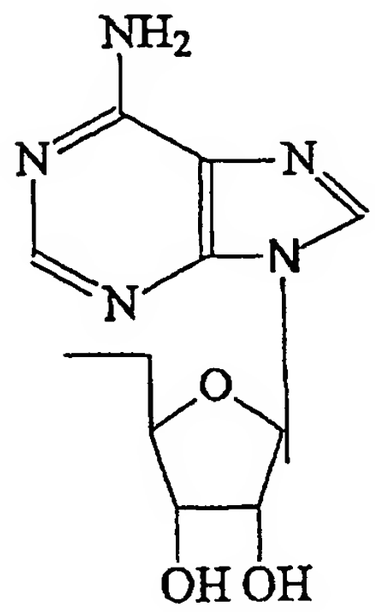


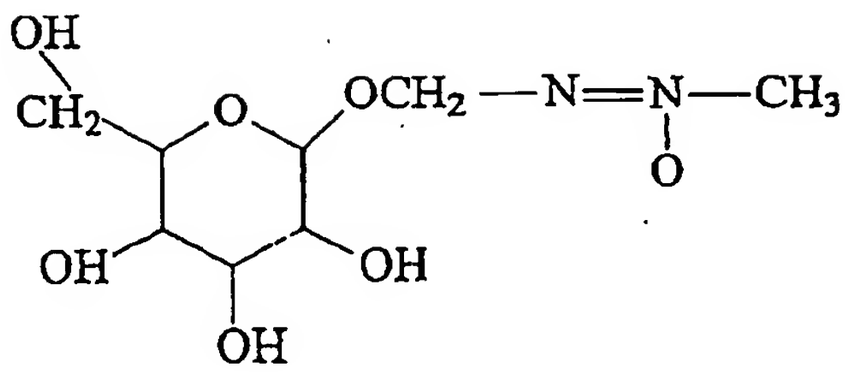
H, CH_3, C_1-C_5 hydrocarbon chain, C_1-C_5 substituted hydrocarbon chain, small hydrocarbon ring or heterocyclic ring, small substituted hydrocarbon ring or heterocyclic ring, citric acid and derivatives thereof, acetic acid and derivatives thereof, ascorbic acid and derivatives thereof, glucouroic acid or derivatives thereof, lactose, sialic acid, monosaccharides or disaccharides of glyceraldehyde, erythrose, threose, ribose, arabinose xylose lyxose, allose, altrose, glucose, mannose, gulose, idose, galactose, talose, or their acidic ketose, alditol or inositol forms, calcium chelating molecule, oxygenated small molecule, any organic molecule that exhibits calcium-binding properties similar to tetracyclin





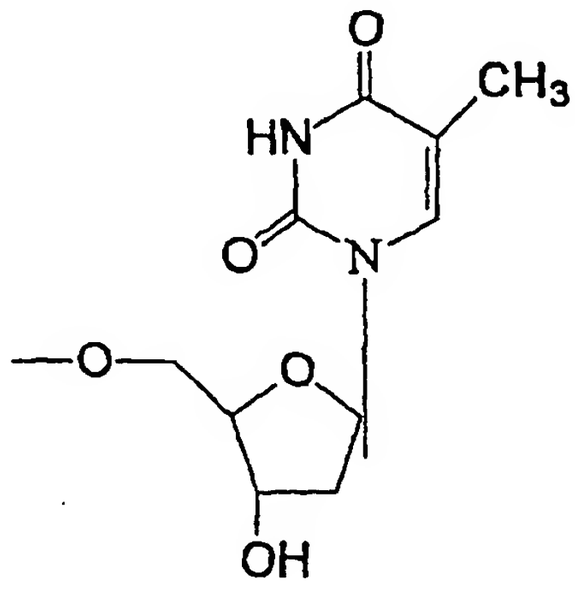
80



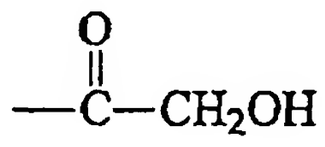


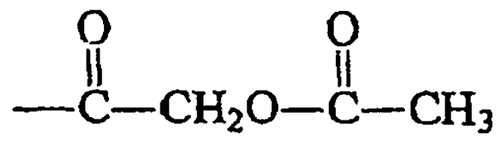
85

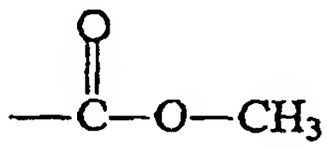
AMENDED SHEET



wherein R_6 is selected from the group consisting of:

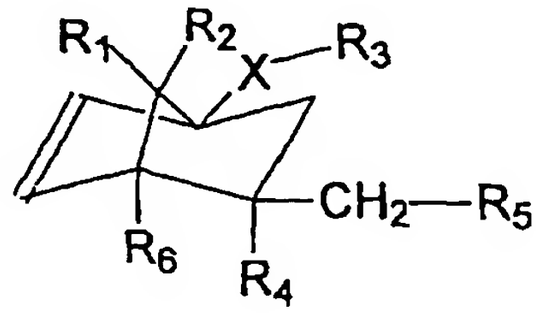






H, CH_3, OH, amine, C_1-C_5 carbo-aliphatic chain substituted with two or three of the following groups selected from the group consisting of: keto, hydroxy, sulfoxy, amide, an amino acid, ethers of the form $-CH_2-O-(CH_2)_n-CH_3$ where n=1-5, wherein the right hand hydrocarbon chain is unsubstituted or substituted with 1 to 5 -OH or carbonyl groups.

15. A paclitaxel compound having a chemical structure



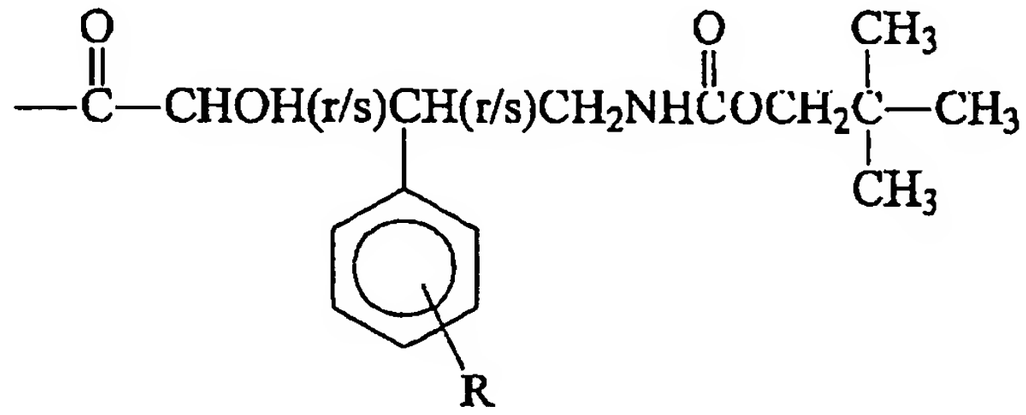
Empfangszeit 5.Sep. 22:17

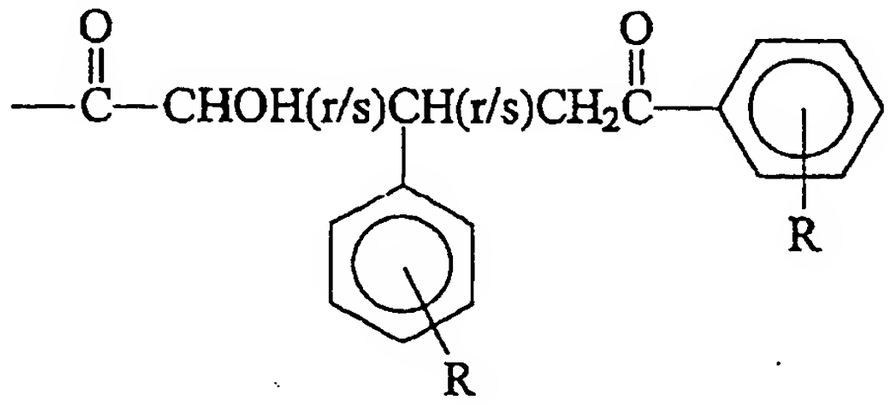
AMENDED SHEET

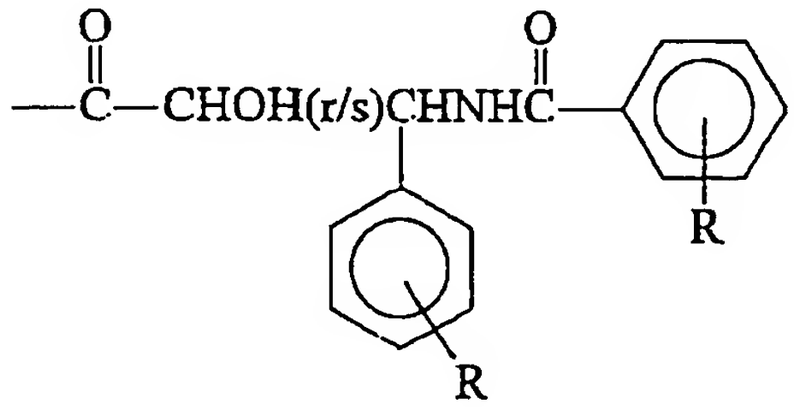
wherein R_1 and R_2 are selected from the group consisting of: hydrogen, methyl, acetyl, ethyl, C_1 - C_4 aliphatic chain and substituted C_1 - C_6 aliphatic chain, wherein said substituted aliphatic chain is substituted once or twice with functional groups selected from the group consisting of: amide, ketone, hydroxy, phenyl, carboxylic acid, and an amino acid;

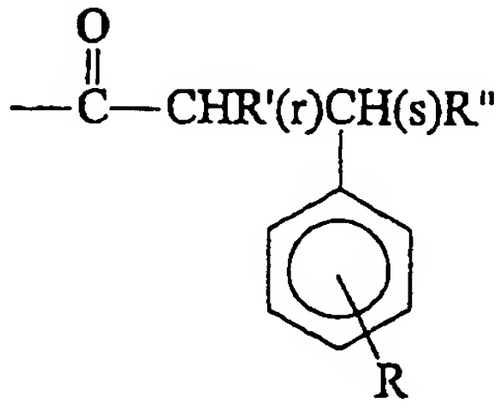
wherein X is selected from the group consisting of: O; CH_2; NH; S; S-CH_2; O-CH_2; or none;

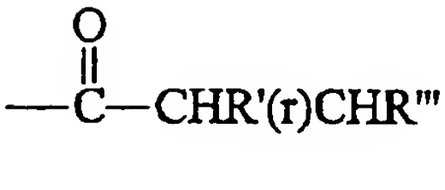
wherein R_3 is selected from the group consisting of:



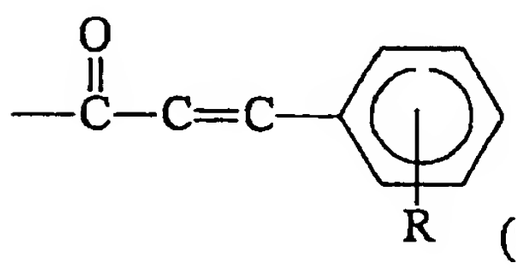




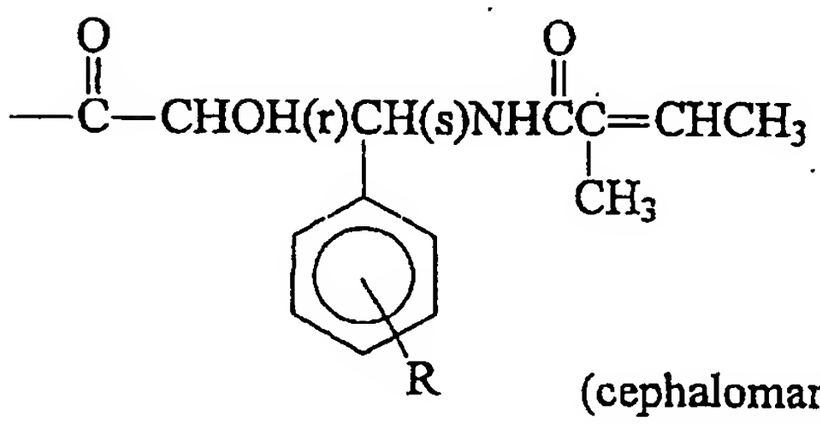




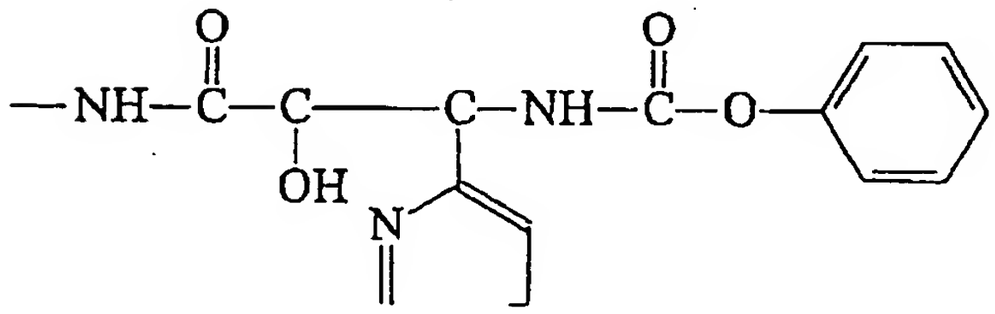
15



(trans)



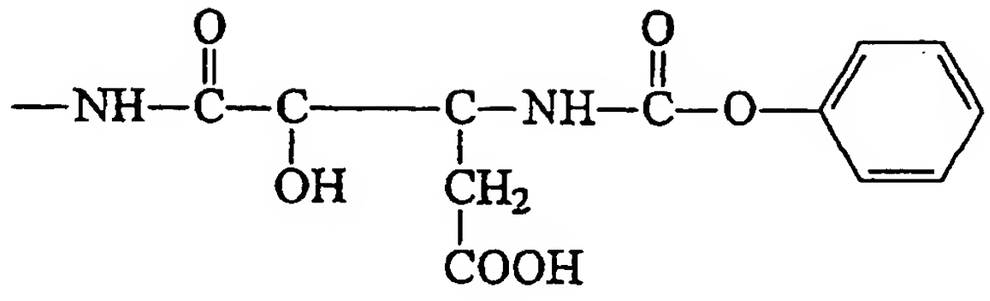
(cephalomannine)

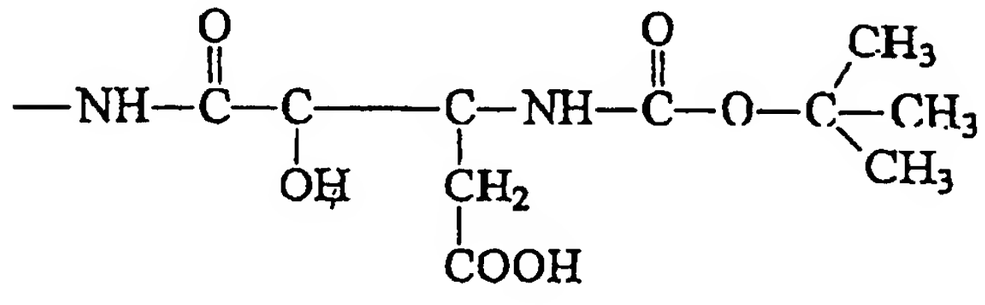


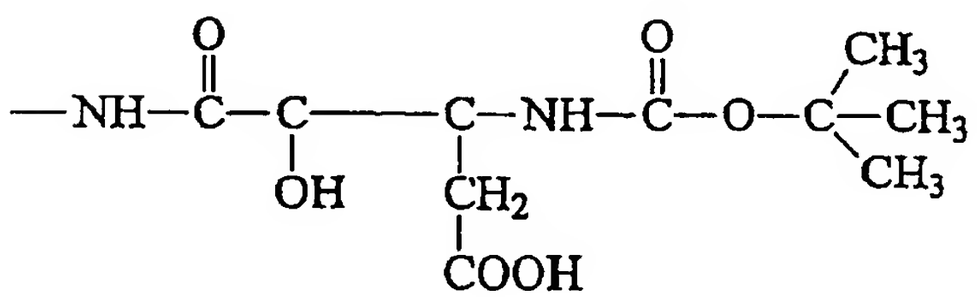
20

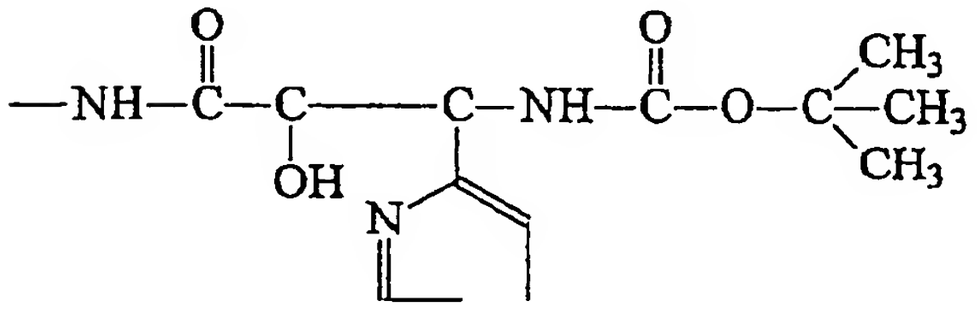
Empfangszeit 5.Sep. 22:17

AMENDED SHEET



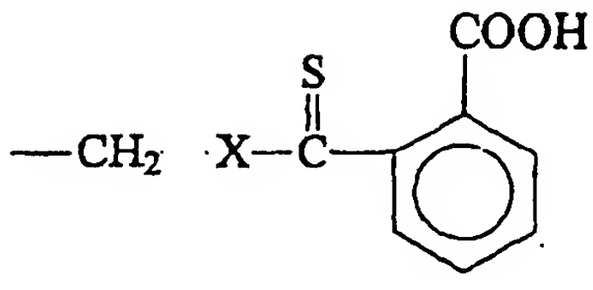


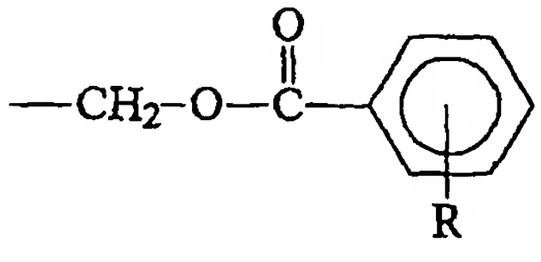


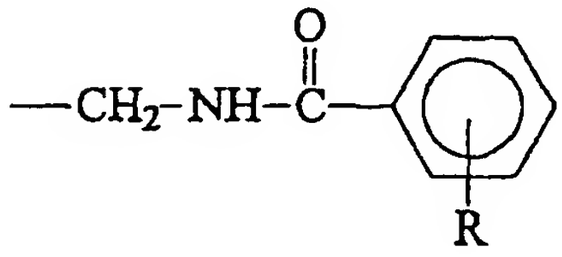


wherein the aryl rings are unsubstituted or singly, doubly, or triply substituted with R selected from the group consisting of: H, OH, and an electron withdrawing substituent;wherein R' is selected from the group consisting of: OH and H; wherein R" is selected from the group consisting of: NHBOC and H; wherein R"' is selected from the group consisting of: singly or doubly substituted aryl and fused aromatic ring;

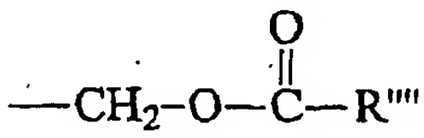
wherein R_4 is selected from the group consisting of:



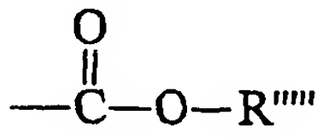




wherein the aromatic ring is singly, doubly, or triply substituted with any electron-withdrawing substituent compatible with the system which provides a lower energy gap in a π - π interaction;



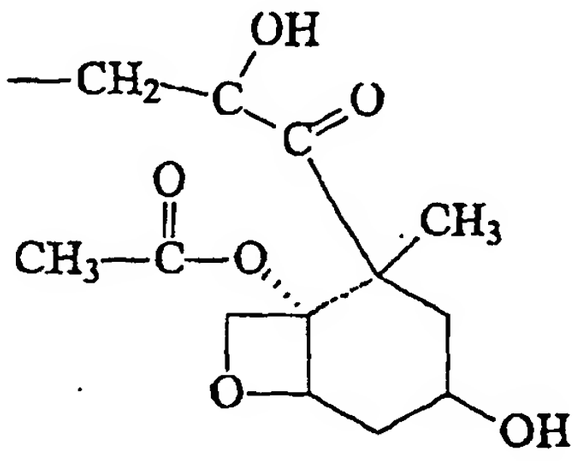
wherein R"" is a fixed aromatic ring or a fused aromatic ring substituted with any electron-withdrawing substituent compatible with the system which provides a lower energy gap in a π - π interaction;



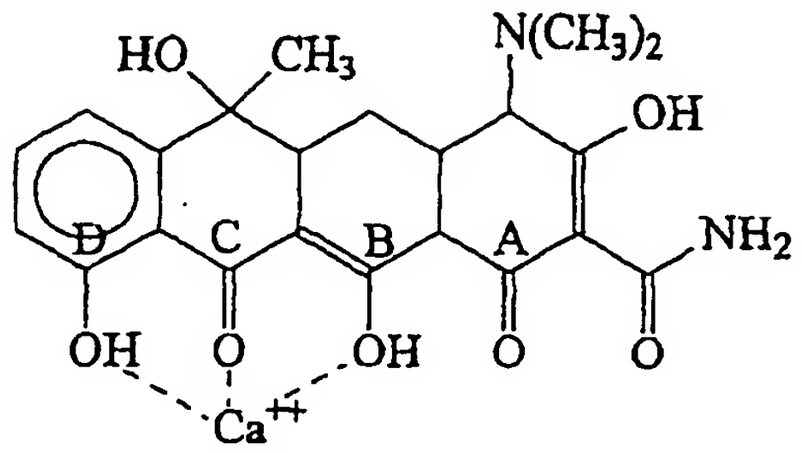
wherein R"" is selected from the group consisting of: H, cyclopropane, C_1-C_3 hydrocarbon chain, and C_1-C_3 substituted hydrocarbon chain wherein said substituted

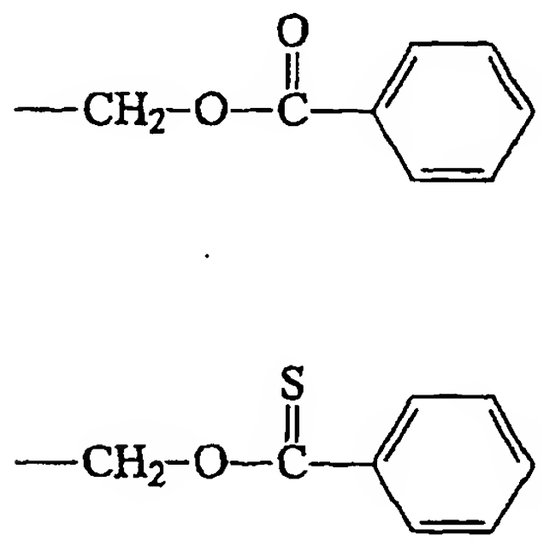
hydrocarbon chain is substituted with any electron-withdrawing substituent compatible with the system which provides a lower energy gap in a π - π interaction;

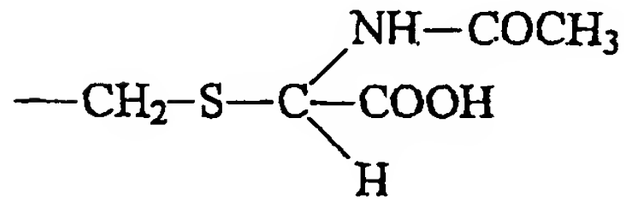
wherein R_5 is selected from the group consisting of:

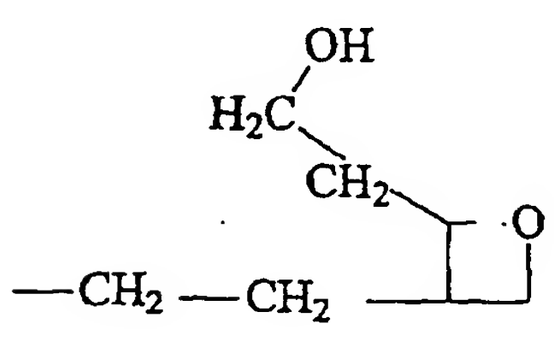


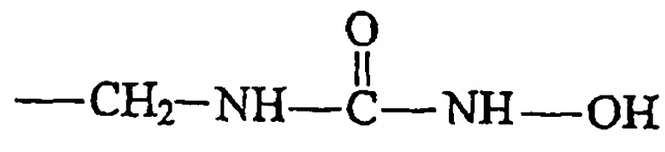
H, CH_3, C_1-C_5 hydrocarbon chain, C_1-C_5 substituted hydrocarbon chain, small hydrocarbon ring or heterocyclic ring, small substituted hydrocarbon ring or heterocyclic ring, citric acid and derivatives thereof, acetic acid and derivatives thereof, ascorbic acid and derivatives thereof, glucouroic acid or derivatives thereof, lactose, sialic acid, monosaccharides or disaccharides of glyceraldehyde, erythrose, threose, ribose, arabinose xylose lyxose, allose, altrose, glucose, mannose, gulose, idose, galactose, talose, or their acidic ketose, alditol or inositol forms, calcium chelating molecule, oxygenated small molecule, any organic molecule that exhibits calcium-binding properties similar to tetracyclin

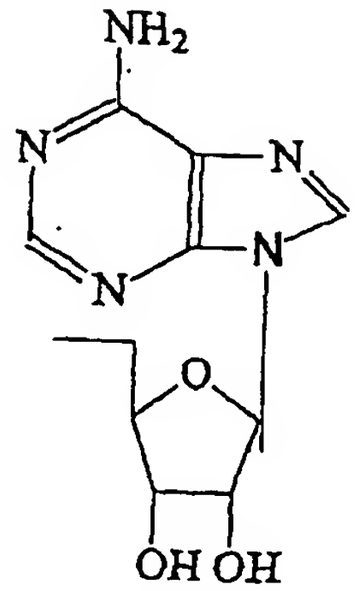


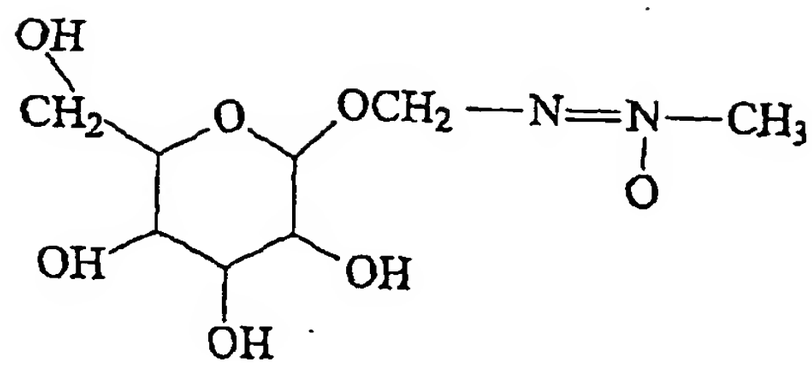




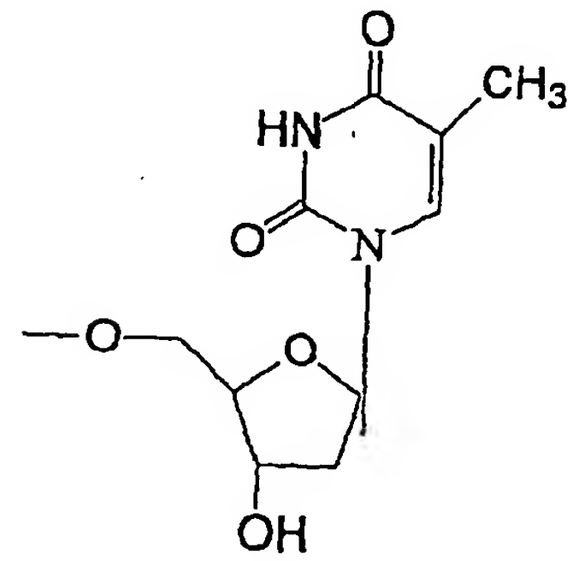




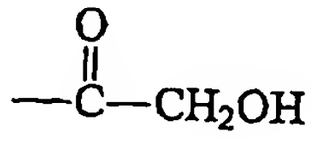




85

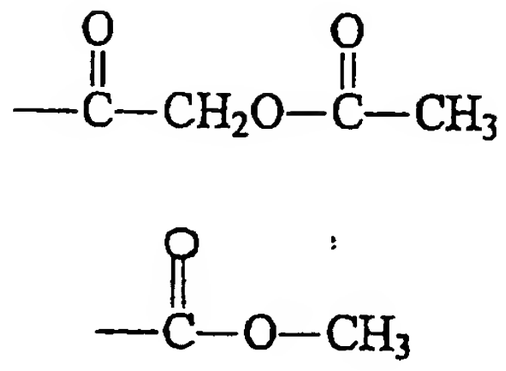


wherein R_6 is selected from the group consisting of:



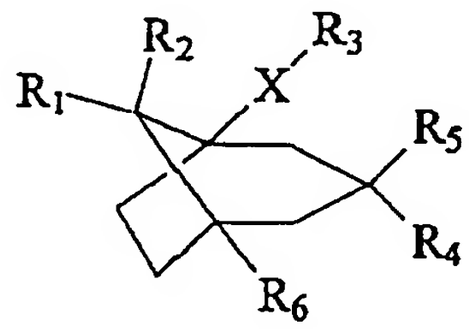
82

AMENDED SHEET



H, CH_3, OH, amine, C_1-C_5 carbo-aliphatic chain substituted with two or three of the following groups selected from the group consisting of: keto, hydroxy, sulfoxy, amide, an amino acid, ethers of the form $-CH_2-O-(CH_2)_n-CH_3$ where n=1-5, wherein the right hand hydrocarbon chain is unsubstituted or substituted with 1 to 5 -OH or carbonyl groups.

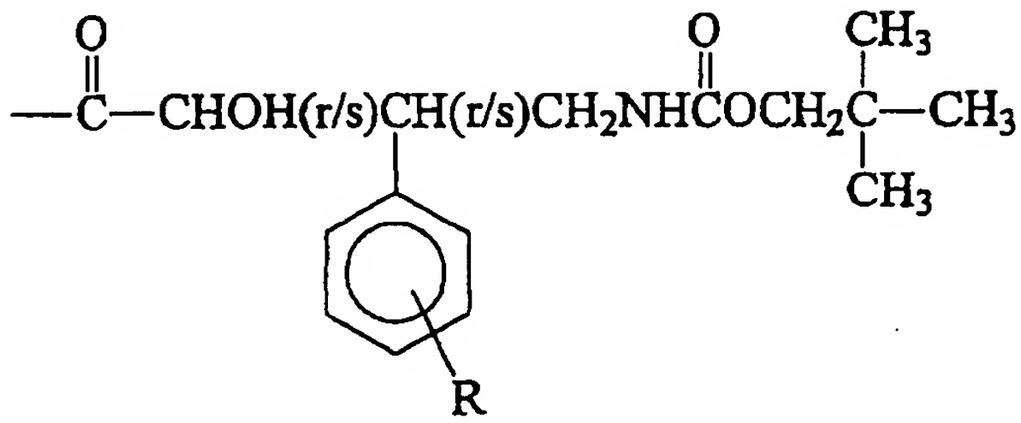
16. A paclitaxel compound having the following bicyclo-octane chemical structure

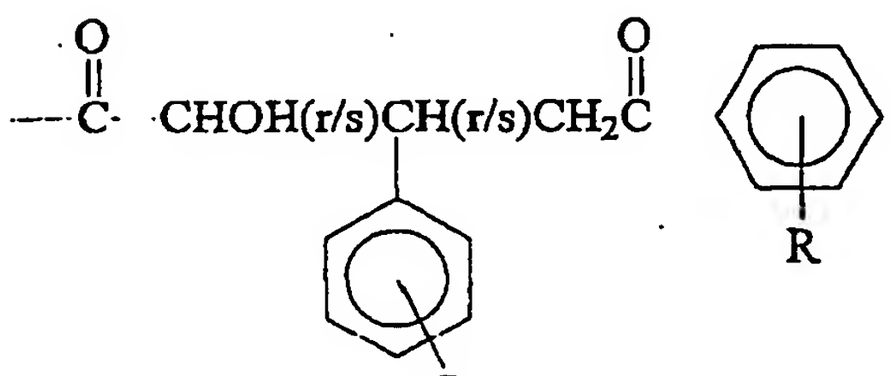


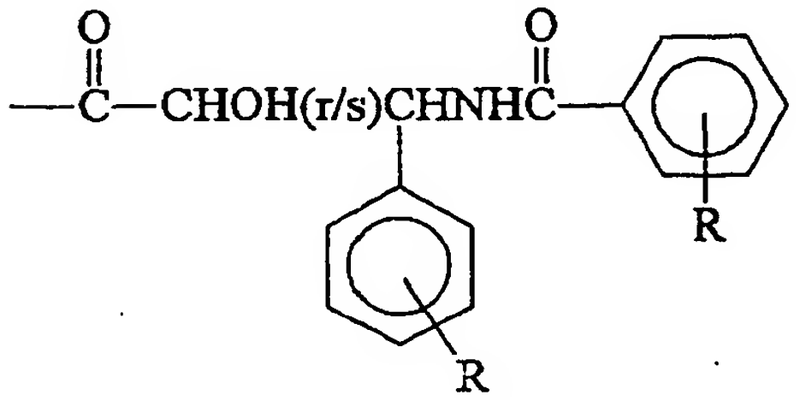
wherein R_1 and R_2 are selected from the group consisting of: hydrogen, methyl, acetyl, ethyl, C_1 - C_4 aliphatic chain and substituted C_1 - C_6 aliphatic chain, wherein said substituted aliphatic chain is substituted once or twice with functional groups selected from the group consisting of: amide, ketone, hydroxy, phenyl, carboxylic acid, and an amino acid;

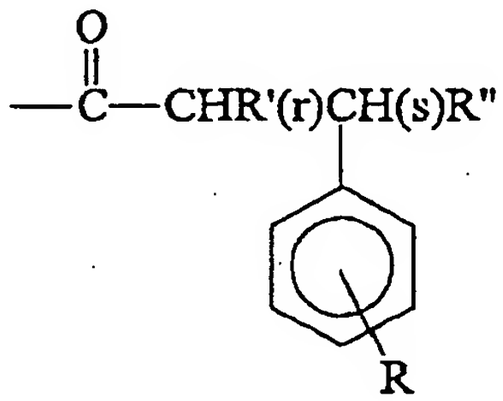
wherein X is selected from the group consisting of: O; CH_2; NH; S; S-CH_2; and O-CH_2;

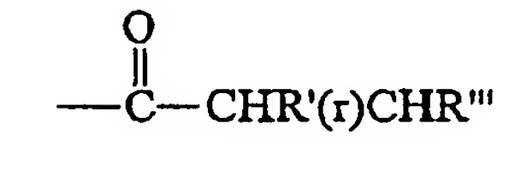
wherein R_3 is selected from the group consisting of:

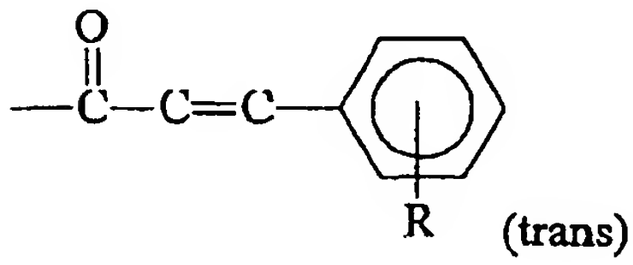




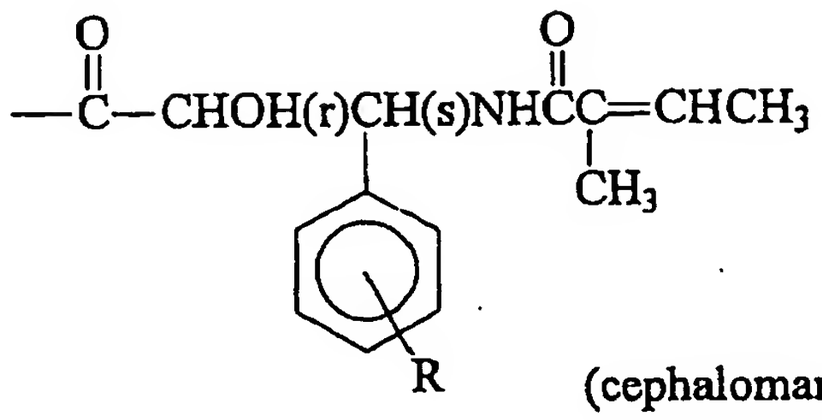




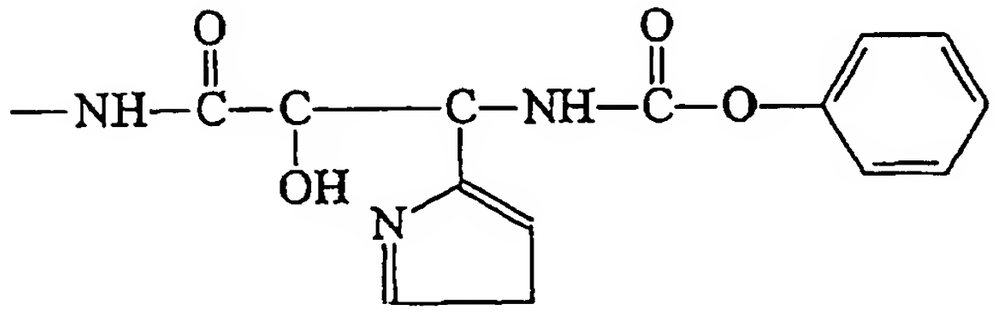


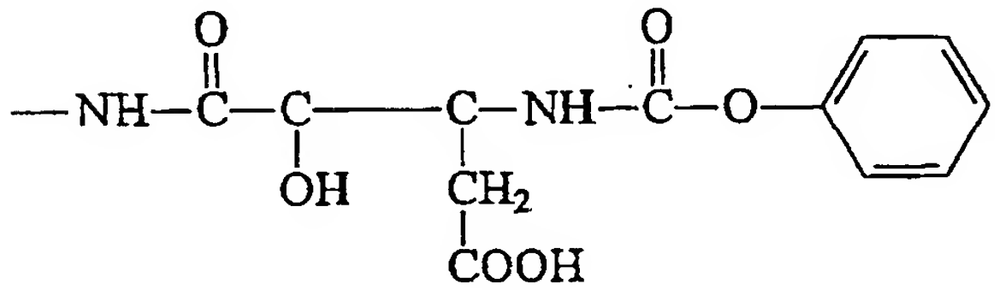


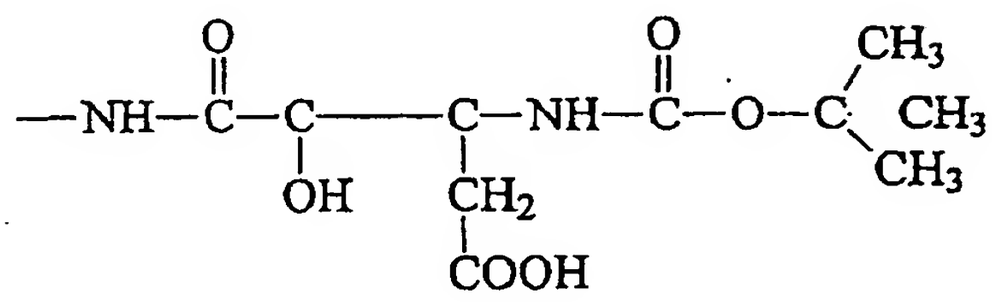
(trans)

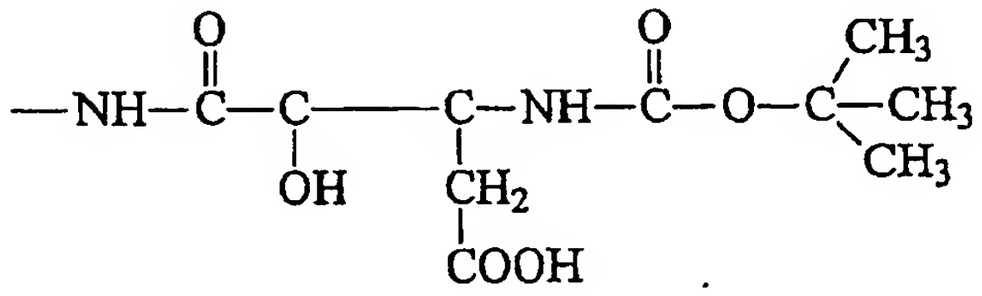


(cephalomannine)

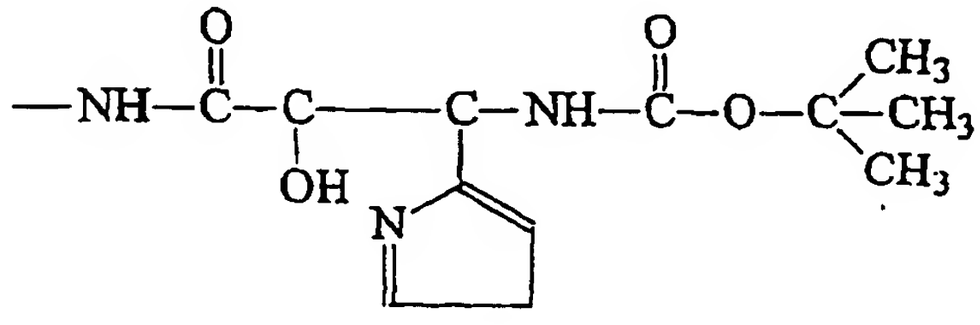






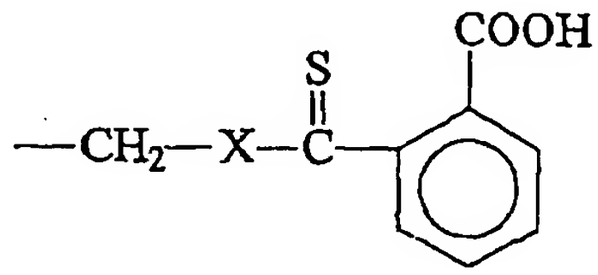


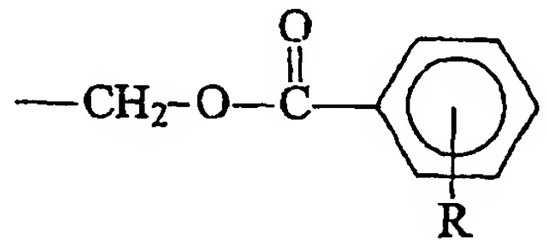
Empfangszeit 5.Sep. 22:17
AMENDED SHEET

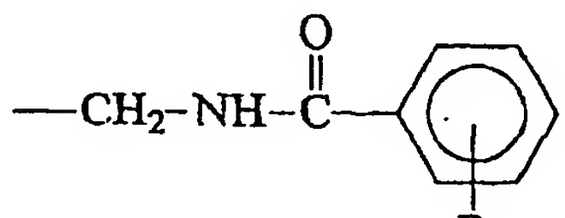


wherein the aryl rings are unsubstituted or singly, doubly, or triply substituted with R selected from the group consisting of: H, OH, and an electron withdrawing substituent; wherein R' is selected from the group consisting of: OH and H; wherein R'' is selected from the group consisting of: NHBOC and H; wherein R''' is selected from the group consisting of: singly or doubly substituted aryl and fused aromatic ring;

wherein R_4 is selected from the group consisting of:

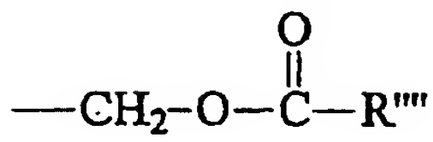




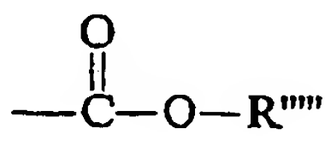


R

wherein the aromatic ring is singly, doubly, or triply substituted with any electron-withdrawing substituent compatible with the system which provides a lower energy gap in a π - π interaction;

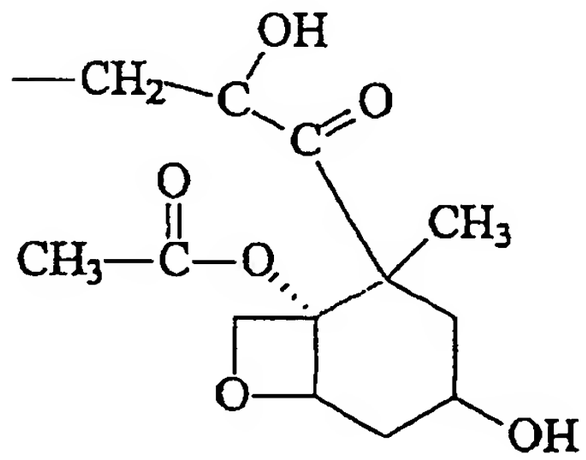


wherein R"" is a fixed aromatic ring or a fused aromatic ring substituted with any electron-withdrawing substituent compatible with the system which provides a lower energy gap in a π - π interaction;



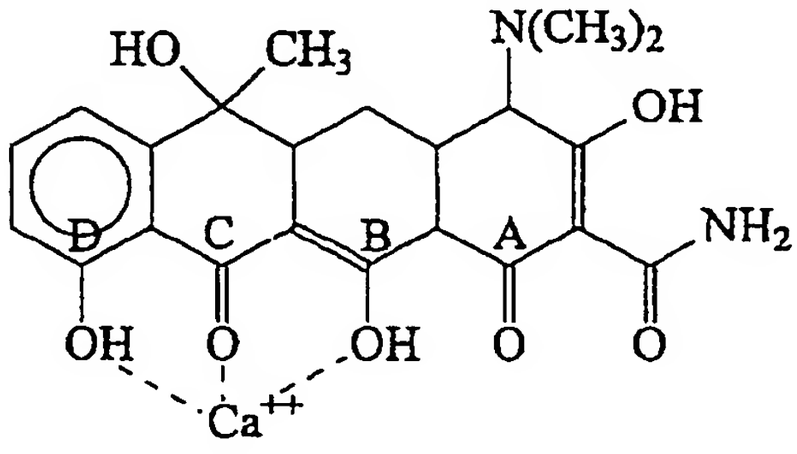
wherein R"" is selected from the group consisting of: H, cyclopropane, C_1-C_3 hydrocarbon chain, and C_1-C_3 substituted hydrocarbon chain wherein said substituted hydrocarbon chain is substituted with any electron-withdrawing substituent compatible with the system which provides a lower energy gap in a π - π interaction;

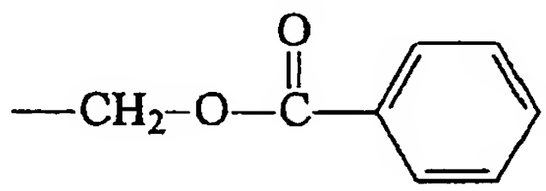
wherein R_5 is selected from the group consisting of:

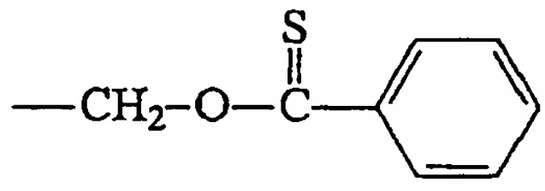


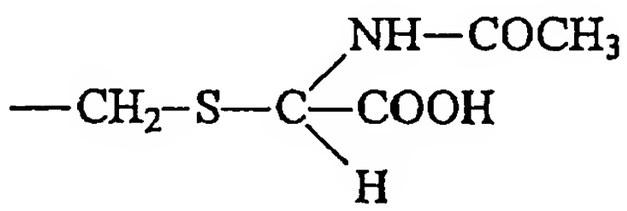
H, CH_3, C_1-C_5 hydrocarbon chain, C_1-C_5 substituted hydrocarbon chain, small hydrocarbon ring or heterocyclic ring, small substituted hydrocarbon ring or heterocyclic ring, citric acid and derivatives thereof, acetic acid and derivatives thereof, ascorbic acid and derivatives thereof, glucouroic acid or derivatives thereof, lactose, sialic acid, monosaccharides or

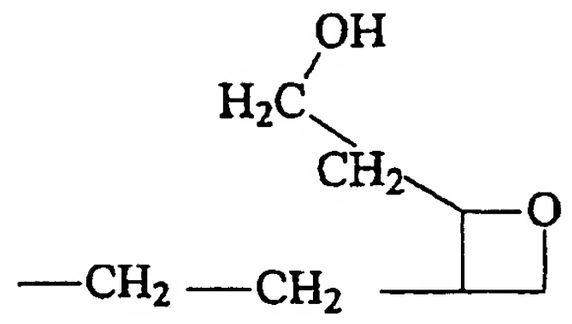
disaccharides of glyceraldehyde, erythrose, threose, ribose, arabinose xylose lyxose, allose, altrose, glucose, mannose, gulose, idose, galactose, talose, or their acidic ketose, alditol or inositol forms, calcium chelating molecule, oxygenated small molecule, any organic molecule that exhibits calcium-binding properties similar to tetracyclin



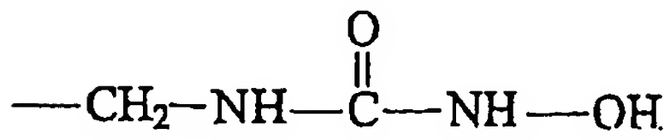


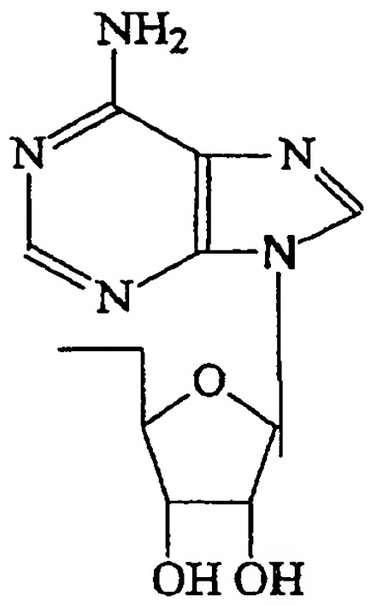


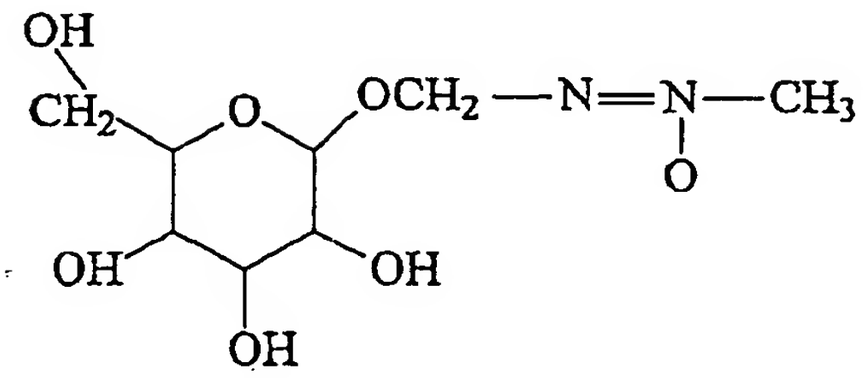




80



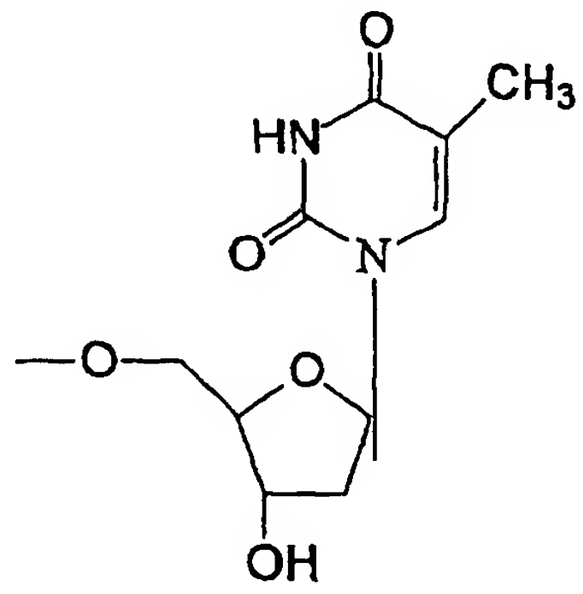




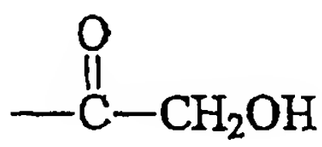
85

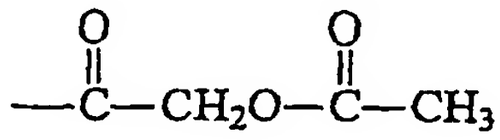
89

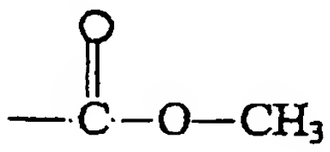
10365/07402



wherein R_6 is selected from the group consisting of:





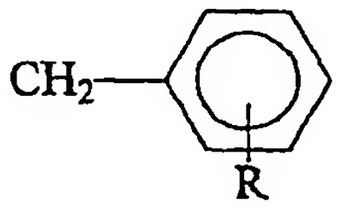


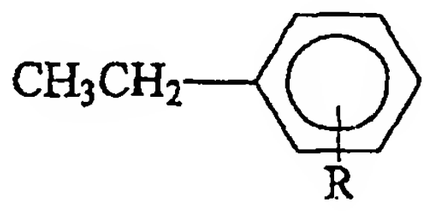
H, CH_3, OH, amine, C_1-C_5 carbo-aliphatic chain substituted with two or three of the following groups selected from the group consisting of: keto, hydroxy, sulfoxy, amide, an amino acid, ethers of the form $-CH_2-O-(CH_2)_n-CH_3$ where n=1-5, wherein the right hand hydrocarbon chain is unsubstituted or substituted with 1 to 5 -OH or carbonyl groups.

17. The compound of claim 12, 13, 14, 15, or 16, wherein the amino acid identity of R_1 or R_2 is selected from the group consisting of asparagine, glutamine, aspartic acid, glutamic acid, threonine, serine and tyrosine.

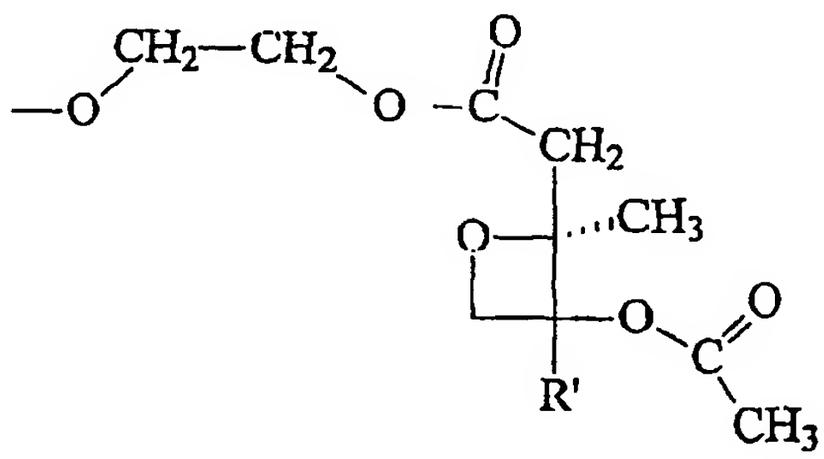
18. The compound of claim 12, 13, 14, 15, or 16, wherein R_1 is chosen from the group consisting of H and CH_3.

19. The compound of claim 12, 13, 14, 15, or 16, wherein R_2 is chosen from the group consisting of CH_3, CH_2OCOCH_3,





wherein R is H or singly, doubly, or triply substituted or fused; and



wherein R' is selected from the group consisting of H and CH_3.

20. The compound of claim 12, 13, 14, 15, or 16, wherein R''' is selected from the group consisting of imidazol ring, tryptophan unsubstituted or substituted with carboxylic acid derivatives.

21. The compound of claim 12, 13, 14, 15, or 16, wherein R_3 is any group derived from the 13 position in taxane's skeleton that exhibits activity toward inhibiting the depolymerization of microtubules or anticancer activity.

22. The compound of claim 12, 13, 14, 15, or 16, wherein the oxygenated small molecule of R_5 is selected from the group consisting of dipeptides of "ASP-ASN", or "GLY-GLN" and the cyclic dipeptide of "PHE-GLN."

23. The compound of claim 12, 13, 14, 15, or 16, wherein the amino acid of R_6 is selected from the group consisting of serine, asparagine, and threonine.